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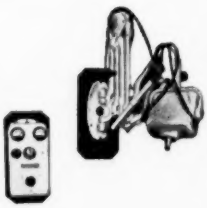

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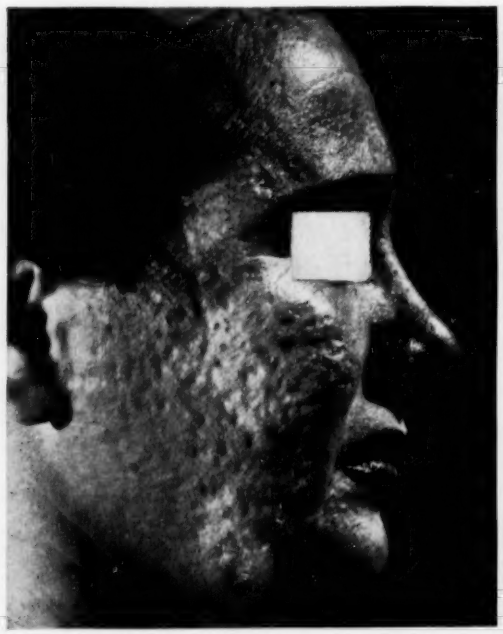

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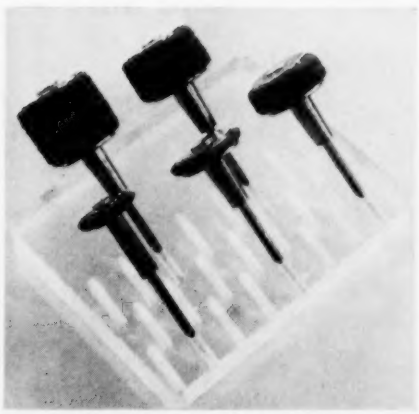

* *Ref.: Kurtin, A. "Corrective Surgical Planing of Skin," October 1953, Arch. Dermat. & Syphil.*

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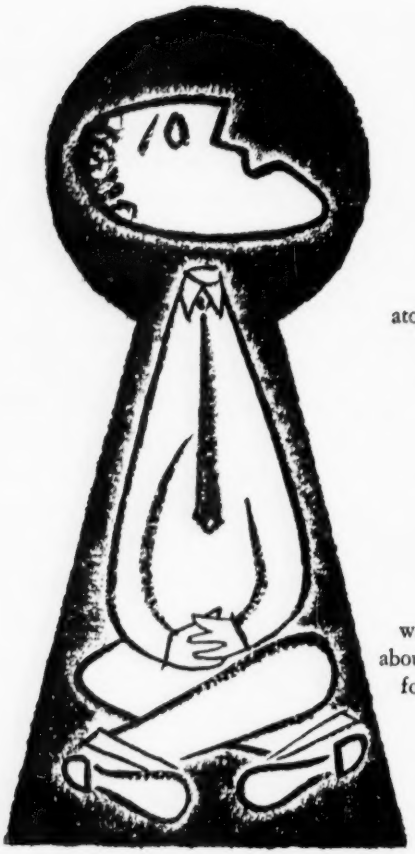

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VOLUME 70 NOVEMBER 1954 NUMBER 5

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OBSERVATIONS ON PORPHYRIA CUTANEA TARDA

LOUIS A. BRUNSTING, M.D.
ROCHESTER, MINN.

PORPHYRIA is a relatively rare, inherited fault of pyrrole metabolism which produces a wide variety of clinical symptoms from time to time or remains latent for years or for life. It is characterized by the excretion of abnormal kinds and amounts of porphyrins, chiefly uroporphyrin and its precursors. The condition also is manifested in certain domestic animals as photosensitivity.

This concept of porphyria must be modified to some extent in the light of recent discoveries. Abnormal excretion of porphyrin is increased in cases of lead poisoning. Furthermore, porphyria of two distinct types has been induced in laboratory animals by administration of phenylhydrazine, lead and ultraviolet light on the one hand, and by allylisopropylacetylcarbamide (Sedormid) on the other. These two experimental forms are similar in many respects to the main types which occur naturally in human beings, namely, the erythropoietic and the hepatic.

The older classifications of porphyria into congenital, acute, and chronic forms were based mostly on clinical characteristics with recognition of some distinguishing features in the excreted porphyrins. Several comprehensive reviews of the subject of porphyria have recently appeared: those by Rimington,[23] Watson,* and Schwartz,[26] all experts in the field of porphyrin metabolism, are especially commendable. The exact position of certain forms of chronic porphyria is still subject to some dispute, particularly that type designated by Waldenström,[30] "porphyria cutanea tarda," in which cutaneous signs of photosensitivity appear late in life as the sole manifestation of the disease, and the "mixed" type of Watson,[32] in which cutaneous signs occur in combination or alternation with abdominal or nervous symptoms, or both.

The unique position of porphyria congenita has been acknowledged by reason of its rarity, the association of a mutilating photosensitivity in childhood with splenomegaly and other evidence of hemolytic disease, and by the concentration in tissues and urine of free uroporphyrin I without evidence of porphobilinogen. Such patients have not been found to be genetically linked with families featuring variants of acute porphyria in large numbers.

Recent contributions by Schmid, Schwartz, and Watson † of the University of Minnesota, have added materially to our understanding of the pathogenesis of porphyria. Utilizing newly developed techniques involving microassay and fluores-

Presidential address at the meeting of the American Dermatological Association, Inc., White Sulphur Springs, W. Va., April 14, 1954.

From the Section of Dermatology and Syphilology, Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

* References 31 and 32.

† References 24 and 25.

cent microscopy, these investigators analyzed the porphyrin content of tissue (mainly bone marrow and liver) from 31 patients with assorted forms of porphyria, as follows: 2 had congenital, 11 intermittent acute, 13 cutanea tarda, 3 mixed, and 2 the latent type. Their evidence supports the concept that porphyria appears in two fundamentally different forms: (1) erythropoietic, in which excessive uroporphyrin and coproporphyrin form in the developing red cells of the bone marrow, and (2) hepatic, in which the liver is regarded as the principal or only site of formation of porphyrin.

In five cases of the rare erythropoietic type, Schmid and co-workers ‡ found normal and abnormal lines of normoblasts in the bone marrow. Normoblasts of the abnormal line exhibited intense red fluorescence with uroporphyrin, predominantly in the nucleus but to a lesser degree in the cytoplasmic fraction also. In addition, special examinations disclosed peculiar inclusions in the nuclei of these

TABLE 1.—*Clinical and Laboratory Features of Porphyria* *

		Hepatic Porphyria	
	Erythropoietic Porphyria	Acute Intermittent	Cutanea Tarda
Synonyms	Congenital or photosensitive	Acute toxic or idiopathic	Chronic
Frequency	< 1%	± 60-70%	± 30-40%
Usual age of onset	Childhood	2d to 4th decade	4th to 6th decade
Signs and symptoms	Photosensitivity (mutilating); splenomegaly and hemolytic anemia, erythrodontia, hypertrichosis, melanosis	Abdominal colic; paresis; psychic disturbances; hypertension; oliguria; constipation; melanosis (?)	Photosensitivity; melanosis; hypertrichosis; violaceous hue; sclerodermoid skin; hepatic dysfunction
Urine color	Red	Port-wine or normal (darkens on standing)	Normal or dark, red occasionally
Porphobilinogen	Absent	Present	Absent
Zinc porphyrin	Absent	Present	Present
Uroporphyrin	Type I	Types I and III	Types I and III
Marrow porphyrin	Markedly increased	Normal	Normal
Liver porphyrin	Slightly increased	Markedly increased (precursor, mainly)	Markedly increased (porphyrin mainly)
Course	Improved by splenectomy	Aggravated by drugs, pregnancy	Aggravated by drugs, alcohol

* Modified from Schwartz.[26]

cells which proved to be hemoglobin. The percentage of normal and abnormal cells varied in the individual cases. This evidence was interpreted to mean that erythropoietic porphyria is essentially a blood dyscrasia with two lines of normoblasts, one of them showing the inborn error of metabolism of porphyria. In a review of the literature on so-called porphyria congenita, Schmid ‡ found only 34 cases in which data were adequate to permit them to be classified as cases of the truly erythropoietic type. Both sexes were affected equally.

In the hepatic group, the porphyrin in the bone marrow was consistently normal. In the cases of intermittent acute porphyria, the urine and liver contained porphobilinogen but little preformed porphyrin. In cutanea tarda, the liver was highly fluorescent with preformed porphyrin; little precursor was found. In the mixed forms, the chemical findings were consistent with those of the hepatic group in general, but varied according to the clinical picture that predominated at the time of the examination.

‡ Schmid, R.; Schwartz, S., and Watson, C. J.: Personal communication to the author.

The distinguishing features of the various forms of porphyria (modified from Schwartz [26]) are presented in Table 1.

In porphyria cutanea tarda, that is, the purely cutaneous type, the onset is at middle age or later and the course is mild but persistent. Hepatotoxic factors are prominent, and functional impairment of the liver is common. Porphobilinogen is absent. In the mixed type, the age of onset may be younger than the average for the group as a whole; the blistering skin reaction is often explosive and directly related to exposure to the sun. Attacks of abdominal or nervous symptoms coincide or alternate with the cutaneous phase or smolder intermittently in the background. Here, too, a familial factor is not uncommon. Porphobilinogen is usually found in the freshly voided urine. This division into types is somewhat arbitrary and often indecisive.

FREQUENCY

The delayed cutaneous phase of porphyria, as it appears for the first time in adult life, is being diagnosed with increasing frequency according to reports in the literature. My colleagues and I have described 21 such cases in previous reports.§

Watson's series [32] of all types of porphyria collected in the past 15 years numbers 160 patients. He observed 71 personally. Twenty-three of the group had cutanea tarda porphyria; 11 had mixed porphyria. Other recent reports in this country have presented scattered examples of cutanea tarda,‖ and mixed forms.¶

During the past year, Bolgert, Canivet, and LeSourd [3] reported 9 typical cases of the cutaneous form from Paris, and Tappeiner [27] 13 from Vienna. Groups of similar cases from Hungary and Argentina have been mentioned previously.[6]

Porphyria is not uncommon in South Africa, and may involve persons of European descent as well as the native Bantu. The latter group, it is said, often manifest the milder cutaneous forms of the disease.[16] In 1951, Barnes [1] reported 40 cases of porphyria, 8 of which were of the delayed cutaneous type. One patient, a girl of 13 with porphyria congenita and splenomegaly, had the rare, erythropoietic type. Her record was described in detail by Findlay and Barnes.[13] A surprising degree of ocular damage occurred in 84 cases of porphyria reported by Barnes and Boshoff.[2]

A most remarkable saga of assorted cases of mixed type of porphyria occurring in family groups of Afrikaners is reported by Geoffrey Dean of Port Elizabeth.[10] The patients may have had a common heritage far back in South African history. In many instances an affected family was first recognized when one of its members suffered an acute attack. Dean recorded a noteworthy example which I have paraphrased:

> A nurse, aged 19 years, died of acute porphyria after laparotomy for supposed intestinal obstruction. The original head of the family, who was remembered as having had blistering and a scarred skin, had died in 1884. His descendants numbered 460 persons throughout five generations. All living relatives were thereupon contacted. Members were regarded as having porphyria if the urinary findings were positive (402 persons tested), or if they showed typical skin lesions and their immediate relatives were proved to have porphyria. In this way, it was found that at least 57 of the family appeared to have inherited porphyria (22 males and 35 females). Fifty-one inherited a sensitive skin that blisters and ulcerates easily. Thirty-nine of the 57 are still alive;

§ References 5 to 7.

‖ References 11, 17, 21, and 34.

¶ References 9, 19, 28, and 29.

excessive excretion of porphyrins was demonstrated in 37 of them. Nine of the group have died with symptoms typical of acute porphyria (eight females and one male); these include two sisters of the original nurse.

Dean's entire series included 13 family groups in which 216 individuals were found to have porphyria. Inheritance was a Mendelian-dominant character. The patients were adults and about an equal number of both sexes were affected, although the acute phases were more common in women between the ages of 19 and 50 years. The ill effects of pregnancy, laparotomy, anesthesia, sedative drugs and alcohol were outstanding. No instances of erythropoietic porphyria were mentioned.

Several interesting cases have been reported from England. Pettit and Anderson [22] described two sisters who presented melanosis, hypertrichosis, and blistering lesions of the arms and legs. The urine was pink and contained uroporphyrin and coproporphyrin. In both cases an unusual rarefaction of the lower end of the femurs was demonstrated on x-ray examination. Discombe and Treip [12] reported an example of the mixed type of porphyria. Their patient, a woman, began to have blisters at the age of 20 years. Later abdominal symptoms and recurrent jaundice developed and she died at the age of 30 years with terminal paralysis. Gazet's [14] patient had recurrent abdominal symptions, jaundice and, for a brief interval, skin lesions. Investigation of the family revealed nine relatives who had porphyria.

Further examples of the mixed type of porphyria have been described by Rimington and co-workers # in a series of papers with elaborate protocols and records of analysis of excreta for porphyrin. The patients were four young men, aged 14 to 30 years, and a young woman, sister of one of them. The five patients manifested severe photosensitive reaction as well as attacks of abdominal colic and frequently jaundice. Rimington emphasized a reciprocal relation between the amount of porphyrin excreted in the urine and the amount excreted in the feces. During remissions, the latter increased, especially that of protoporphyrin, while the urine became practically free of uroporphyrin. In this respect, Rimington considered porphyria cutanea tarda to be distinct from intermittent acute porphyria.

CLINICAL SURVEY OF THIRTY-FOUR CASES

Porphyria cutanea tarda is commoner in this country than is generally appreciated. Since 1944, when our first case was recognized, a total of 34 such patients, 26 men and 8 women (Cases 1 to 34), with the characteristic clinical and laboratory features of the disease have been seen at the Mayo Clinic by my colleagues and me. Data on the first 21 cases of this group have been reported previously.*

In almost all instances, the skin disease was the major complaint. Hypertension was not an uncommon finding on physical examination, but no evidence of hemolytic disease was found.

The majority of the patients in this series are classified as having porphyria cutanea tarda because the signs of the disease appeared on the skin for the first time at middle age or later and they remained limited to the skin. In this group, none of the symptoms usually associated with intermittent acute porphyria could be elicited. The urine contained abnormal amounts of porphyrins, but no porphobilinogen.

References 8, 15, 20, and 33.

* References 5 to 7.

Certain of the patients, however, including five men and two women, excreted porphobilinogen in the urine at one time or another, and some had colics or neurologic symptoms in addition to the cutaneous manifestations. One such example was described previously,[6] and his record is now being brought up to date:

CASE 2.—The patient, a man of 20 years, moderately addicted to use of alcohol, first complained of mild blistering and erosion of the skin of his face and hands in the summer of 1946. In November of that year, he had a severe episode of acute porphyria, with red urine, colic, nausea, vomiting, fever, hypertension, and delirium. Blood pressure was elevated, and the test for liver function showed complete retention of the dye although jaundice was not present. At the height of the attack, an edematous, bullous reaction appeared over the face and hands without exposure to sunlight. The eroded portions of skin and mucous membranes were fluorescent and appeared orange-red under a Wood light. Porphyrins were demonstrated in the erythrocytes and plasma, and large amounts appeared in the urine and in the only two specimens of feces that were passed during the acute illness. The patient lost 40 lb. (18.1 kg.) during the 2 weeks of the attack, but recovery was uneventful. The patient has been seen at intervals subsequently. He passed an army physical examination in 1950. At present he is uncomfortable in the sun, but the skin shows only a tendency to scuff easily when injured. Recent examination of urine

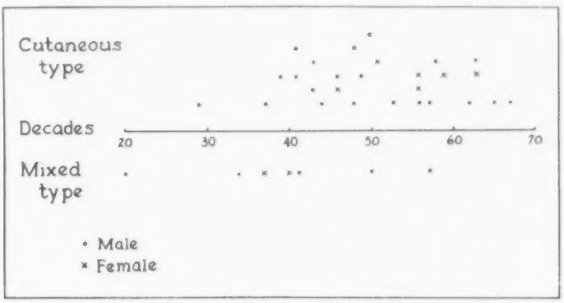

Fig. 1.—Age of patients at onset of symptoms and type of porphyria present.

and stools showed abnormal porphyrins but in lesser amounts than in 1946. The patient is still addicted to alcohol; a late sulfobromophthalein test of liver function shows 6% of the dye retained.

Other patients with the mixed form of the disease have colics or nervous symptoms with cutaneous signs but none of such dramatic character.

None of the 34 patients in this series recalled symptoms of sensitivity to the sun or blistering in childhood. The cutaneous signs first became evident in 31 of the patients after they were 37 years old; in 5 of them, after they were 60; and the oldest, not until he was 67. The distribution of the patients according to sex, type of manifestation, and age at onset of symptoms is shown in Figure 1.

PRECIPITATING FACTORS IN 34 CASES

Heredity.—Data on the familial incidence of porphyria in this series of patients are inadequate. An exhaustive survey by symptoms and by urinalysis of members of families in which the disease appeared was impractical. Nevertheless, a few interesting relationships were brought out by brief sampling. In seven instances, other members of the family were considered to have porphyria, on the basis of

historical evidence or by clinical and laboratory confirmation. The familial occurrence was proved in four cases (Table 2). Various forms of the disease occurred in the same family. There was no record of consanguinity in the parents.

Syphilis.—Two patients had had neurosyphilis, well treated and arrested.

Diabetes.—Five patients, all men, had had diabetes mellitus for several years prior to the onset of symptoms of porphyria; three of these had diabetic neuropathy. In two others, without glycosuria, the glucose tolerance test disclosed abnormally high concentrations of blood sugar but there was evidence of hepatic dysfunction. In addition, one parent of each two nondiabetic patients was said to be diabetic. This association of two genetically controlled disturbances of metabolism may be more than coincidental.

Alcoholism.—Twenty-four of the 34 patients admitted the use of alcoholic drinks in considerable amounts for periods of months or years before the onset of symptoms of porphyria. This was true of three of the eight women in the series. Seven patients denied the use of alcohol. However, six of these seven had evidence of impaired hepatic function.

TABLE 2.—*Familial Porphyria*

Patient		Familial Incidence of Porphyria	
Number	Sex and Symptoms	Relation	Symptoms
1	F Cutaneous	Sister *	Latent (uroporphyrin in urine; no porphobilinogen)
2	M Mixed	Mother *	Latent (porphobilinogen in urine)
4	M Cutaneous	Mother and brother	History of abdominal colics
8	M Cutaneous	Brother and sister	History of death associated with chronic and acute abdominal colics
16	M Mixed	Brother *	Blistering of hands for 15 yr.; onset age 51; alcoholic (uroporphyrin in urine; no porphobilinogen)
18	F Mixed	Sister *	Observed in attack of acute abdominal porphyria, P.O. (uroporphyrin and porphobilinogen in urine)
		Father	Blistering hands for 10 yr. before death at age 68 (history)
		Paternal grandmother	Blistering hands many years in adult life (history)
20	M Mixed	Father	Abdominal colics for many years; died aged 42; in one such attack (history)

* Porphyria proved.

Hepatic Impairment.—Nineteen men and six women showed some degree of functional impairment of the liver; this usually was closely related to the degree of alcoholism. The conventional sulfobromophthalein test showed retention of more than 20% of the injected dye in 5 cases, less than 10% in 11, and none in 7. One man had cirrhosis with ascites in association with the cutaneous signs of porphyria. The serum bilirubin was not elevated to a significant degree in any case and no instances of jaundice were observed.

Long-term management and observation of several patients indicated improvement in hepatic function when the intake of alcohol was discontinued.

Sedatives and Anesthetics.—The well-known adverse effect of drugs of the barbiturate series was observed in a few patients who had the mixed form of porphyria, but in no instance were the cutaneous lesions influenced. One patient

(Case 17) with mild cutaneous lesions, hysteroid behavior, and severe headaches, became unconscious for 24 hours after the subcutaneous injection of phenobarbital sodium.

CUTANEOUS FEATURES IN THIRTY-FOUR CASES

The characteristic low-grade blistering and erosive tendency of the light-exposed surfaces of the skin, with melanosis and violaceous hue, have been described previously.[6] Hypertrichosis was observed in seven women; three men said that the beard hair had thickened so that shaving was difficult. Two men had fuzz which was apparent over the ears.

Fig. 2 (Case 4).—The exposed surfaces of the face and neck show diffuse thickening of the skin, with scarring, superficial abrasions, and increased pigmentation.

Hyperpigmentation was common and was a diffuse process or mottled; sometimes it was associated with vitiligo of the hands. Six patients had red hair and sandy complexions which freckled and burned after exposure to the sun without tanning. Three patients, two men and one woman, mentioned having had red hair in childhood which turned black at puberty. This feature also occurred in the case of Turner and Obermayer.[29] This suggests the existence of some fundamental metabolic or endocrinal derangement in the early life of the patient with porphyria.

Sclerodermoid yellowing and hardening of the exposed skin of the face and back of the neck were of common occurrence in the men and were found in three of the women. In a few instances, punched-out craters and healed scars were observed about the cheeks and back of the neck; these were sharply limited to the area above the collar line (Figs. 2, 3, and 4).

Blistering was an irregular feature, occurring mostly on the fingers and hands, and was not too closely identified with exposure to direct sunlight. Certain patients, however, blistered in sunlight; these were usually women with the mixed type of porphyria. It was not possible to reproduce blistering by test exposure of the skin to artificial light or direct sunlight.

Histopathology.—From 10 patients one or more specimens were obtained from blisters in various stages of development and from thickened areas of chronic indurated skin from the neck and cheek. A more detailed study of this material will be reported subsequently.

Microscopic examination revealed that the bulla was usually of the subepidermal type as a consequence of tension or pressure. The overlying keratin layer was thickened and showed parakeratosis. Cellular material in the bulla was scarce;

Fig. 3 (Case 25).—A severe degree of scarring of the face and neck, sharply delineated at the collar line; scattered abrasions and ulcers; diffuse pigmentation and suffusion of the head and upper trunk, are shown.

acantholysis was not seen. In four specimens, at the base of the bulla, villiform projections of dermal papillae, containing dilated capillaries, were seen to rise irregularly from the floor in a festooned arrangement as described by Bolgert and associates.[3] The upper cutis showed a moderate, inflammatory reaction. The elastic and collagen fibers were merged to give the characteristic tinctorial reaction of senile skin. In some instances the walls of the blood vessels showed hyaline thickening (Fig. 5*a*).

Microscopic examination of specimens of sclerodermoid skin showed increased melanosis as a rule; amorphous deposits occurred in the cutis, irregularly outlined, staining bluish with hematoxylin and eosin, and staining yellow with van Gieson's stain. In the centers of these masses, collagen and elastic fibers were disorganized and merged so as to be indistinguishable. Special elastic tissue stains showed fragmentation and tangling of the elastic tissue into purplish clumps at the borders and

beneath the homogeneous zones. Stains for amyloid were negative. This is the picture of the change in skin after chronic light exposure, including the so-called senile skin, which was emphasized in a previous paper [6] (Fig. 5*b*).

A positive periodic acid-Schiff reaction was seen in certain sections of tissue, in the granular layer and midzone of the epidermis, in the amorphous masses in the cutis, and, to some extent, in the thickening hyalin-like walls of the deeper capillaries, but deposits of glycogen were not outstanding as they were in the case of Wells and Rimington.[33] Similar staining reactions have been reported recently by Lobitz and Holyoke [18] in specimens of skin subjected to traumatic irritation with adhesive tape. The deposits of glycogen, then, are probably a response to an irritant of indefinite character. Apparently none of the microscopic changes observed here in the skin are specific for porphyria.

Fig. 4 (Case 6).—The dorsum of the hand shows several bullae, infected abrasions, and hyperpigmentation.

Examination of 10 unstained specimens (embedded in paraffin and also those deparaffinized) under the fluorescent microscope, using a 100-watt light source through a Corning filter, no. 5113, showed no evidence of fluorescent material. These negative results may have been due to inadequate light source, the loss of porphyrins in the preliminary fixing process, or the absence of fluorescent material in the first place. Further studies are in progress.

No porphyrins were demonstrable in the analysis of the blister fluid.

PHOTOSENSITIVITY

Wells and Rimington [33] demonstrated a blistering and edematous reaction of the hand in a man with porphyria cutanea tarda after exposure to natural sun through windowglass (above 3,200 A.), and by exposure to a carbon arc light source (3,500 to 4,100 A.). These coincide well with the range of the absorption

bands of the porphyrins (around 4,000 A.). The patient's serum was fluorescent and contained protoporphyrin. This is the first valid demonstration of photosensitivity in cutaneous porphyria. So far, it has not been possible to confirm this effect in the lower-grade cutaneous reaction observed in the patients of this present series.

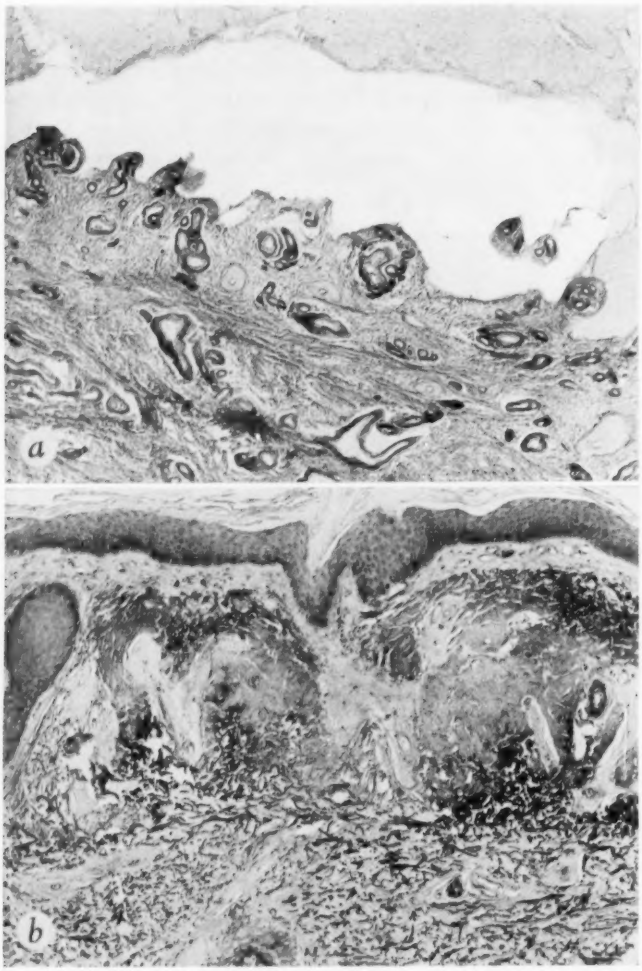

Fig. 5.—(*a*) Dorsum of finger (Case 4). Subepidermal bulla, relatively acellular, is shown. Papillary bodies are projected in festooned arrangement at base of bulla. Dilated blood vessels in upper cutis show thickened walls and positive periodic acid-Schiff reaction (× 70). (*b*) Side of neck (Case 20); Homogeneous, colloidlike deposits are found in the cutis. In these zones, the elastic and collagen fibers are merged as in senile skin. Above and below, the elastic fibers are fragmented and clumped (aldehyde fuchsin-toluidine blue stain; × 60).

The mechanism of the photosensitive reaction in porphyria is not clearly understood.[4] Blistering on exposure to the sunlight does not generally occur in the commonest forms of the disease, the intermittent acute type, although more or less

pigmentation is the rule. It is assumed that the photosensitive reaction in porphyria erythropoietica and in prophyria cutanea tarda is related to the presence of the highly sensitizing uroporphyrin I. In the acute types, the porphyrins are present chiefly in the form of precursors. With the newer technical methods which utilize microassay and fluorescent microscopy, this question may soon be solved.

Porphyrins are suspected of being involved in photosensitive mechanisms of other diseases in man, such as pellagra, in which fluorescence of hepatic tissue has

TABLE 3.—*Long-Term Excretion of Porphyrin in Porphyria Cutanea Tarda*

Case, Age, Sex, Type	Clinical Features	Date	Porphyrins, Mg. per 24 Hr.					
			Urine			Feces		
			Uroporphyrin	Coproporphyrin	Porphobilinogen	Uroporphyrin	Coproporphyrin	Protoporphyrin
Case 2 20M (Mixed)	Mild blisters and erosions; alcoholic. Severe colic for 2 wk. Severe blistering reaction. (Mother has latent porphyria.) Few skin signs. Mild erosions, uncomfortable in sun.	9/13/46	0	0	Tr.	...	....	...
		11/ 3	5.7	7.0	++	...	....	...
		11/ 7	...	...	..	Tr.	44.9	...
		11/10	9.4	13.4	+++	...	....	...
		11/15	...	...	..	Tr.	61.7	...
		11/18	1.4	4.5	0	...	....	...
		2/27/47	1.4	5.4	+	...	....	...
		4/25	0	3.8	0	...	....	...
		10/10	0	3.4	+	...	....	...
		8/28/50	0.6	1.1	+	...	....	...
		11/16/53	0.7	2.0	+	...	....	...
		1/26/54	...	...	..	7.0	1.0	2.0
Case 4 37M (Cutaneous)	Sclerodermoid skin; blisters, erosions, alcoholic, violaceous hue. Red hair turned black at puberty. Skin unchanged.	3/15/47	10.3	2.5	0	...	....	...
		3/19	9.0	1.8	0	...	....	...
		3/22/54	6.2	4.2	0	1.8	8.5	1.6
Case 28 56F (Cutaneous)	Sclerodermoid; mild blisters and erosions. Skin unchanged.	2/ 6/53	6.1	...	0	...	....	...
		10/ 7	2.6	2.0	0	1.8	....	...
		2/28/54	1.3	2.0	0	9.2	10.9	6.3
Case 20 42M (Mixed?)	Sclerodermoid skin; erosions, mild blisters. Red hair turned black at puberty. Infectious hepatitis (1944). (Father died of colics at age 42.) Skin unchanged.	8/ 5/49	6.3	1.3	0	...	....	...
		11/ 1/50	18.6	3.0	+	...	....	...
		2/18/51	11.2	5.7	+	...	....	...
		10/22	13.0	4.7	0	...	....	...
		3/12/52	6.9	2.4	0	...	....	...
		11/ 5	3.3	7.6	0	...	....	...
		11/ 7	7.7	3.2	0	...	....	...
		4/21/53	4.2	3.3	0	...	....	...
		2/16/54	5.3	3.6	0	7.8	12.1	3.7
Case 12 65M (Cutaneous)	Mild blistering and erosion; violaceous hue; alcoholic; old CNS lues; BSP dye retention 32%. Mild erosions; BSP test normal.	4/14/48	6.8	2.3	0	...	....	...
		6/28	4.5	1.6	0	...	....	...
		10/19	1.4	...	0	...	....	...
		7/17/50	1.2	0.2	0	...	....	...
		6/20/51	0.6	0.3	0	...	....	...
		11/17/53	0	3	0	...	...	...
		3/20/54	0	0.1	0	0	1.8	1.2

been demonstrated. In Southdown sensitivity and facial eczema in sheep and cattle, phylloerythrin from chlorophyll has been incriminated as the sensitizing agent. Photosensitivity has been observed in calves, but not in sheep, after administration of phenothiazine as an anthelmintic. It is due to the transformation of the drug into a toxic product which sensitizes to light. Some such mechanism may obtain in the production of photosensitivity in human beings with the development of porphyria cutanea tarda.

EXCRETION OF PORPHYRINS

As a general rule, patients with porphyria cutanea tarda excrete large amounts of preformed porphyrins in the urine and feces, and no porphobilinogen. The urine usually contains uroporphyrin (Waldenström type, a mixture of isomers I

and III, zinc complex) and coproporphyrin; the feces contain uroporphyrin, coproporphyrin and, sometimes predominantly, protoporphyrin. Uroporphyrin may be absent from the urine and feces in some instances, but excessive amounts of coproporphyrin are usually present. The analyses for porphyrin were done in the laboratory of Dr. Harold L. Mason.

Excretion of urinary porphyrins has decreased in some but not in other cases followed for several years. Long-term observations in five cases are recorded in Table 3.

Patients with mixed symptoms excreted porphobilinogen in the urine in variable amounts at times but not always. On the other hand, in a few patients who manifested low-grade cutaneous lesions and nothing more, traces of porphobilinogen were found in the urine. In these cases, sampling may have been inadequate.

Data on fecal porphyrins in this series are not sufficient to confirm or deny Rimington's contention that a reciprocal relation exists between the excretion of urinary and fecal porphyrin according to the presence or absence of symptoms, with the fecal porphyrins predominating in remission. In the low-grade phase of porphyria cutanea tarda, it is difficult to judge remission. At least in borderline cases, in which urinary findings are inconclusive, it will be well to examine the porphyrin content of the feces. Watson [32] found an appreciable amount of porphyrin in the feces of patients with acute porphyria during stages of remission.

COURSE AND TREATMENT

In porphyria cutanea tarda, the skin lesions are generally mild but persistent. Avoidance of exposure to sunlight is helpful, but most important is elimination of the damaging insult to the liver by the strict avoidance of alcohol or hepatotoxic drugs. In some instances, the clinical picture remains unchanged over a period of years, while large amounts of porphyrins are drained through the excreta. The patients in this series have received no demonstrable benefit from the use of folic acid, vitamin B_{12} or riboflavin.

Now and then, in women, the degree of hypertrichosis is seen to diminish but the sclerodermoid features, once they appear, seem to be permanent.

SUMMARY AND CONCLUSIONS

The subject of porphyria, with the recent advances based on chemical distinctions and the localization and sites of origin of the porphyrins, is reviewed briefly. The two main types of porphyria are discussed, the erythropoietic and the hepatic types. The latter is divided into intermittent acute and chronic or cutaneous forms.

The clinical and laboratory characteristics of 34 patients of the chronic cutaneous type of hepatic porphyria observed over the past nine years are summarized in this paper. Twenty-seven of these had porphyria cutanea tarda, seven the mixed form in which cutaneous symptoms were combined with abdominal or nervous symptoms, or both, at various times.

In this series, males predominated, and the cutaneous symptoms appeared late in life as the presenting signs of the disorder. A familial incidence was noted, and several examples are cited. A possible relationship to diabetes was also noted.

The incidence of functional impairment of the liver as well as the incidence of alcoholism was high in the group. Alcohol may have a hepatotoxic influence on the precipitation and maintenance of symptoms.

The clinical appearance of the chronic cutaneous features suggests photosensitivity, but a relationship has not been proved. The distinctive violaceous hue which frequently occurs is unexplained. Disturbance of pigmentation usually occurs; in some of the patients, early in life.

Histopathologic examination of the affected skin shows a benign type of blistering, as well as degenerative changes in the cutis, but these are not distinctive for porphyria.

A few long-term observations on porphyrin excretion are presented.

The literature indicates that porphyria cutanea tarda is commoner than is generally appreciated, the number of cases recognized depending on the awareness of the observer. The exact position of the disorder in relation to acute porphyria is not settled.

Dr. Harold L. Mason and Miss Louise Reichrath, his technical assistant, performed the chemical analysis of porphyrins.

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DERMATOLOGICAL ASPECTS OF CRETINISM

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ALTHOUGH cretinism is primarily a problem of endocrinology, hypothyroidism developing early in life produces a number of physical, physiologic, and pharmacologic changes of interest to the dermatologist. Many of these abnormalities respond promptly to thyroid therapy, but others apparently involve degenerative changes and are permanent in character.

The material on which this paper is based consisted of eight sporadic cretins, two goitrous cretins, and four cases of childhood myxedema. In keeping with the usual sexual distribution, 11 patients were females and 3 males. Our youngest patient was 8 years old; the oldest was 47. Although 13 of the patients were white, with various European origins, the 14th was a Negro. All of the white patients were born in eastern Pennsylvania; the Negro girl was a native of South Carolina. Mentally, two were morons, five were imbeciles, and seven were idiots. All were patients at the Pennhurst State School for the feebleminded, Spring City, Pa. The phlegmatic disposition of the cretins gave rise to much better cooperation than the mental status of the patients would suggest. The laboratory and x-ray findings were consistent with the clinical pictures presented. Most of the patients had received an undetermined amount of thyroid extract early in life; but, with the exception of one case of childhood myxedema, none had received thyroid medication within two years of the time of commencement of this study.

In this work, the physical findings, physiologic and pharmacologic responses, and cutaneous histopathology of the untreated cretins were compared with similar observations in those having had a minimum of 75 days of thyroid medication. In administering thyroid extract, the following was given daily: A thyroglobulin preparation (Proloid),* 0.03 gm. during the first week, 0.06 gm. during the second week, 0.1 gm. during the third week, and 0.13 gm. throughout the remainder of the period of observation. As several of the patients were unable to take 0.13 gm. of thyroid daily, these were given slightly smaller amounts.

The skin of cretins is usually cool, coarse, and quite dry, although three of our sporadic cretins and one of the cases of childhood myxedema had a normal amount of moisture on the skin. After thyroid therapy, six patients developed moisture of the

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* The Proloid used in this study was furnished by the Warner-Chilcott Laboratories.

axillae; and three, in the submammary region. This moisture seemed to increase as treatment was prolonged. Fine wrinkling of the extremities was noted in four instances.

Of the 13 white patients studied, 6 had bronzed skin; the others had a pasty white color. Under thyroid therapy, all patients tended to develop a normal flesh appearance. A yellowish tinge to the palms, said to be due to carotinemia in cretins, was present only in the Negro girl. In 13 of the patients, the skin was loose. In four of them, it seemed to be too large for the underlying structures. This "oversize" was most evident on the extremities. The skin of two young patients appeared thin on palpation; but in 11 older patients, it was thick and spongy. This apparent thickness of the skin, however, was an illusion; upon removing specimens of skin from various parts of the body for histologic examinations, it was found to be thin, with fat extruding from the wound. Scaling, so frequently mentioned by other authors, was present in none of our cases. Firm stroking, however, would leave in its wake a line of dry scales. Institutional diet and hygiene, perhaps, explain the lack of scaling in this series of cases.

The variations in the hair in cretinism are interesting. Eight of the patients had black hair, five had dark brown hair, and one goitrous cretin had red hair. The hair of 4 patients was normal in texture; on the other hand, 10 had coarse hair, although there was no correlation between color and texture. Though 10 had a normal amount of hair, two had slightly less than normal, while that of the remaining 2 was definitely sparse. One patient's hair came down over the upper half of the forehead. Twelve had straight hair; the Negro girl had the kinky hair of her race, and one sporadic cretin had dark brown hair that was slightly curly.

The eyebrows were normal in seven patients. In five cases, an abundant amount of hair in the glabellar region joined the eyebrows of the two sides. Two had sparse hair on the outer parts of the eyebrows.

In regard to the hair on the face, five were hairless, five had the normal amount of lanugo, and four exhibited the lanugo confined to the upper lip. The two male patients old enough to have a beard showed only a moderate amount of lanugo.

The trunks of six patients were hairless. One had lanugo on the back only. Two had a normal amount of lanugo, while three sporadic cretins, one goitrous cretin, and one case of childhood myxedema had an excessive amount of hair on the back.

All of the sporadic and goitrous cretins exhibited absence of axillary hair. The hair of the axillae in the cases of childhood myxedema was sparse in two cases and normal in two cases. In all the cases of childhood myxedema pubic hair was abundant. Of the remaining 10 patients, the pubic hair was scant in 6 and absent in 4, of whom three were under 13 years of age.

There was no correlation between the presence or absence of hair on the extremities, fingers, and toes. The extremities were hairless in seven, had slight hair in two cases, and exhibited normal hair in five patients. The hair on the fingers had the same incidence, although its occurrence did not parallel its presence on the extremities. Hair was even less frequent on the dorsal surfaces of the toes, being absent in 10 patients, sparse in 2, and normal in 2. Of those exhibiting hair on the toes, three were cases of childhood myxedema, and one was a sporadic cretin. No

changes were noted in the distribution or amount of hair following four months of thyroid medication.

Contrary to popular belief, the nails of all of our patients, except one, were normal in texture. Atrophy and brittleness were generally not evident; however, the nails of one sporadic cretin appeared thinner and more fragile than normal. The nails tended to be short, broad, and flat in keeping with the wide stubby hands of these patients. The whitish crescents at the base of the nails were normal in six but absent in eight cases. Of the latter, three developed lunulas of the thumb only after 80 days of thyroid medication. An interesting change noted was pallor of the proximal halves of all nails in six cases, but of the proximal two-thirds of the great toe nails only in two cases. The nails of four of these patients became a uniform pink after 80 days of thyroid therapy.

The tongue could be classified as normal in size in one sporadic cretin and in one case of childhood myxedema. Although the remainder appeared large, two exhibited the typical scrotal pattern, while one was unusually pale.

The lips were pale, thick, coarse, and protuberant in 11 cases. Fissuring was present in only one patient in contrast with its frequent occurrence in Mongolism. Minor scaling showed on the lips of one patient.

In most of our cases, there were excessive amounts of fat about the face, nape of the neck, supraclavicular regions, hips, and mons veneris.

COLD PRESSOR TESTS

Cretins tolerate cold poorly. In warm weather, they frequently prefer to wear sweaters; in winter, they spend considerable time near radiators. Because of these observations, it was thought that cold pressor studies might be informative. Following the method of Hines,[1] we took a basic blood pressure reading obtained during a 20-minute rest period in the supine position. The right hand was then placed in a bucket of water containing ice. Blood pressure readings were taken on the left arm at the end of 30 and of 60 seconds following immersion; the higher of these compared with the basic level. In this test, an elevation above the basal level of more than 20 mm. Hg in systolic pressure and of more than 15 mm. Hg in diastolic pressure indicates a hyperreactive type of response.

It was impossible, because of the patient's resistance, to apply a blood pressure cuff to 5 of our 14 patients. Six cooperated fully; five of these showed no change in blood pressure during the test; whereas the sixth had a 4 mm. Hg drop in systolic pressure and 2 mm. Hg drop in diastolic pressure. In the three patients who cooperated poorly, the blood pressure rose from 6 to 18 mm. Hg systolic pressure and 8 to 18 mm. Hg diastolic pressure.

Three months later, after 80 days of thyroid therapy, the 6 cooperative patients gave essentially the same results. The patients who had cooperated poorly before had found confidence in the investigator and remained quiet during the tests. The maximum increase in blood pressure in the latter group was 8 mm. Hg systolic pressure, while there was no change whatsoever in the diastolic pressure.

Comparing these results with those in normal controls and the work of others, one finds it reasonable to conclude that, before or after thyroid therapy, cretins and cases of childhood myxedema are hyporeactors to cold as applied in these tests.

ULTRAVIOLET LIGHT

Applying an Alpine ultraviolet quartz lamp (Luxor model, Hanovia Chemical and Mfg. Co.) at a distance of 24 in. (60.9 cm.) to the backs of six normal controls, it was determined that the minimum erythema dose was 15 seconds. When it was applied to the backs of 12 cretins, the minimum erythema dose was found to be as follows: 15 seconds, one patient; 30 seconds, three patients; 45 seconds, one patient; 60 seconds, three patients; and 90 seconds, one patient. Three cretins showed no erythema even at 90 seconds.

In regard to pigmentation following ultraviolent light, four controls showed pigmentation at all test sites exposed from 15 to 90 seconds; on the other hand, two exhibited pigmentation at sites receiving 30 to 90 seconds of radiation. Among the cretins, two showed pigmentation at 60 seconds and upward; one, at 75 seconds, and two at 90 seconds, while seven showed no pigmentation whatsoever. The erythema and pigmentation following ultraviolet light seemed independent of whether the skin was bronzed or pasty white.

After thyroid therapy, the patients exhibited a smaller minimum erythema dose and a greater tendency toward pigmentation after they had ultraviolet light; i. e., a trend toward normal. When applied to the backs of treated cretins, the minimum erythema dose was found to be 15 seconds, one patient; 30 seconds, five patients; 45 seconds, two patients; and 60 seconds, one patient. One showed no erythema even at 90 seconds; on the other hand, two were no longer available for study.

In regard to pigmentation, one treated cretin showed pigmentation at 30 seconds and upward, five at 60 seconds, one at 75 seconds, and one at 90 seconds. Two showed no pigmentation whatsoever; two were no longer available for study.

In summarizing, one finds that untreated cretins react less than normally to ultraviolet light both in regard to erythema and subsequent pigmentation. After thyroid therapy, there is a shift toward the normal in that the minimal erythema dose is decreased and pigmentation is greater following ultraviolet light.

TRAUMA

After firm strokes on the backs of 12 patients, a trail of loose epithelial cells was left in the wake of the blunt instrument. Seven congenital cretins and one case of childhood myxedema developed only red streaks. One congenital cretin showed a red streak and slight whealing; on the other hand, two of these cases of childhood myxedema and one sporadic cretin gave the triple response of Lewis. No material difference in the outcome to firm stroking was noted after 80 days of thyroid therapy.

On the other hand, histamine phosphate, 1:1000, injected intradermally or introduced into the skin of the back by the multiple pressure method employed in smallpox vaccinations, produced in all patients local dilatation at the site of injection, a red flare and wheal formation, in that order. In view of this normal response to histamine, one might postulate that most cases of long-standing hypothyroidism fail to liberate normal amounts of H-substance in the skin following trauma.

SWEATING

Cretins obviously perspire less than normal persons. An attempt was made to estimate this difference quantitatively, using the method of Silverman and Powell.[2] In this procedure, the part to be tested is painted with quarter-strength tincture of ferric chloride, dried by means of an electric fan, then placed for three minutes in contact with paper impregnated with tannic acid, 5%. In the presence of moisture, a black color occurs. Tests were made on controls to determine the amount of discoloration to be considered normal. Applying this method to the study of the palms of eight cretins, I found that three showed no sweating of the palms at all and five exhibited sweating in amounts from a trace to about one-half that of our controls. When the tests were repeated on the epigastrium, four cretins showed no sweating at all; three, a trace of perspiration and one, sweating approximately 50% of that of our controls. There was no correlation between the sweating of the palms and epigastrium. Pilocarpine hydrochloride, 5 mg., administered hypodermically failed to alter the amount of perspiration of the palms and epigastrium. In fact, the only change noted after this amount of pilocarpine was sweating of the forehead in one patient.

When larger doses of pilocarpine hydrochloride, 8 mg., were administered hypodermically, every one of 12 patients showed sweating of the face; 8, sweating of the axillae; 1, of the groins; 2, of the submammary regions; 1, generalized; 2, of the soles, and 4, of the palms. Sweating of the palms was not produced in any person who had shown absence of sweating by the ferric chloride and tannic acid technique.

Sweating of the palms and epigastrium, as determined by the ferric chloride and tannic acid test, was not influenced by two months of thyroid therapy. After the hypodermic administration of 5 mg. of pilocarpine hydrochloride to treated cretins, however, they exhibited a definite increase in sweating of these areas. In fact, considering other areas of the body, pilocarpine hydrochloride, 5 mg., administered hypodermically to treated cretins produced slightly more sweating in the same places than did 8 mg. of pilocarpine hydrochloride given to untreated cretins. One may conclude, therefore, that thyroxin increases the response of the sweat glands to the cholinergic affect of pilocarpine.

Pilocarpine hydrochloride, 5 mg., administered hypodermically in the back of a normal individual results in wheal formation and an area of erythema. When it was given to 12 of our untreated cretins, areas of erythema, 3 by 3 cm. and 3 by 4 cm. in size, respectively, occurred in two individuals. Two patients exhibited small pink papules at the sites of injections, but the other eight patients showed no reaction whatsoever. When 8 mg. of pilocarpine was given hypodermically, the number showing erythema was increased to five.

After the administration of thyroid to cretins for three months, the cutaneous vessels seemed more responsive. Following the hypodermic administration of pilocarpine hydrochloride, 5 mg., in the backs of our cretins, all but one developed erythematous patches. In general, the erythema was brighter and more extensive. Papules occurred at the site of injection in two cases only. These observations suggest that the local vascular response to pilocarpine is increased in cretins by the administration of thyroid gland.

Pilocarpine hydrochloride, 0.5 mg., administered intradermally into the flexor surface of the forearm at the junction of the middle and upper thirds, produced whealing and erythema, but no sweating in untreated cretins. After three months of thyroid therapy, the results were identical in every respect.

METHACHOLINE CHLORIDE

Methacholine chloride (Mecholyl), 1:500, when it was applied by means of iontophoresis to the backs of 12 of the patients in the study using an electrode of 5 sq. in. (32.3 sq. cm.) with 5 ma. of current for five minutes, produced moderate erythema and gooseflesh in 9 patients. Two cases of childhood myxedema and one sporadic cretin evidenced much sweating in the treated area in addition to the erythema and gooseflesh.

When we administered the same technique to the nonsweating palms of three congenital cretins, methacholine produced a moderate erythema but no sweating.

On the other hand, 0.1 cc. of methacholine, 1:100,000, injected intradermally into the flexor surface of the forearm at the junction of the middle and upper thirds produced whealing and a prompt mild erythema in all of the aforementioned patients. The erythema lasted 30 to 40 minutes, but the wheals disappeared sooner in some cases. No pseudopods, gooseflesh, or sweating were noted, even being absent in the three patients who had perspired freely beneath the electrode when the methacholine was introduced by iontophoresis. Identical results were obtained with intradermal methacholine when the patient had had 80 days of thyroid therapy.

EPINEPHRINE

Epinephrine, 1:1000, applied to the skins of cretins by iontophoresis, using an electrode of 5 sq. in., and 5 ma. current for five minutes, produces a nevus anemicus-like pallor surrounded by a zone of erythema. Injected intradermally in the strength of 1:10,000 into the flexor surface of the forearm at the junction of the middle and upper thirds, epinephrine produces whealing, an area of blanching, pseudopods, and a zone of erythema, but no sweating in the area of blanching. Only in the absence of sweating did the reactions differ from those in normal subjects. After 80 days of active thyroid therapy, epinephrine still failed to produce sweating when injected intradermally, although all of the changes described above as occurring in the untreated cretin were noted.

HISTOPATHOLOGY

In excising sections for histologic examination, I noted that, although it felt thick, the skin was actually thin; and fat would frequently extrude from the wound. Specimens were removed from the loose skin of the forearm and the nonsweating palms; others from a hypertrichotic area of the upper back and lower lip. Additional specimens were removed from the hairless axilla and the pubic area exhibiting little hair in a cretin with regular menses. Further biopsies were done in the supraclavicular regions before and one hour after 150 TRU of hyaluronidase intradermally. The changes produced by this substance were so minimal, however, that they will not receive further consideration. In all, eight portions of skin were studied in the untreated cretins; and seven specimens, after 80 days of thyroid therapy. The latter were taken close to the sites of the earlier biopsies.

Certain changes were found to be consistent throughout the slides studied. The findings on the specimens from untreated cretins may be summarized as follows (Dr. Herman Berman):

Many of the sections demonstrated a thinning and even atrophy of the epidermis (Fig. 1). The stratum mucosum was for the most part quite immature and contained many cells that demonstrated intracellular edema. This change was not localized in any part of the specimen or any part of the mucosum. The granular layer was generally increased in thickness. The granules themselves were very

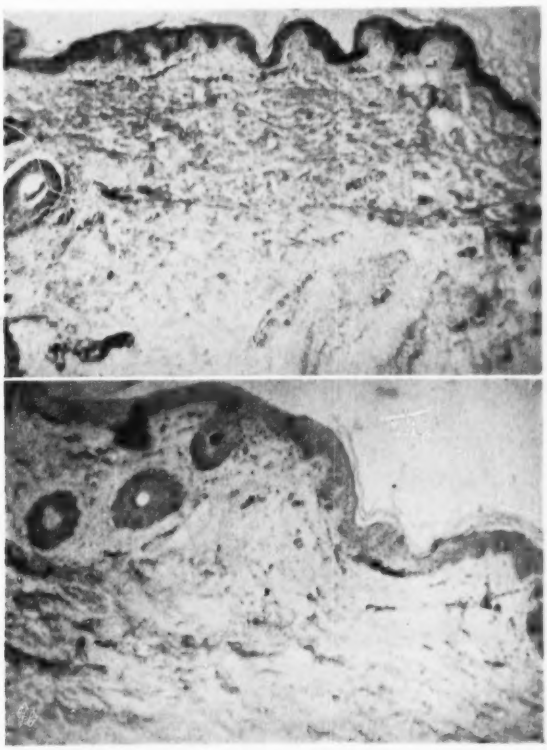

Fig. 1.—Sections from the upper back of a cretin before and after thyroid therapy.

closely packed and took an intense basophilic stain. Immediately over this layer was a dense homogeneous thin sheet of keratin, and above this, the keratin assumed a flaky and basketweave character. Plugging of the follicular orifices was noted in several specimens.

The corium was generally much thinner than normal (Fig. 2). There was a varying amount of edema throughout, but true myxedematous change was not an outstanding feature in any section. The collagen was definitely not normal by reason of the splitting, separation, and shattering of the bundles and fibers, probably the result of edema. Elastic tissue degeneration was the one outstanding feature noted in most of the sections.

Appendages were present, but sparse. No sebaceous or apocrine structures were noted; in addition, the follicles that were seen had cellular elements similar to the immature-appearing epidermis.

Review of the slides of specimens taken close to sites of previous biopsies after 80 days of active thyroid therapy revealed many significant changes. The epidermis of many sections, thin and even atrophic in the untreated patients, was now of normal thickness. Definitely more layers of cells and interpapillary pegs were present in the prickle cell layer. The granular layer was thinner and less prominent. Hyperkeratosis was considerably reduced, approaching or actually becoming normal in almost all specimens. Keratotic plugging of the follicular orifices was now absent.

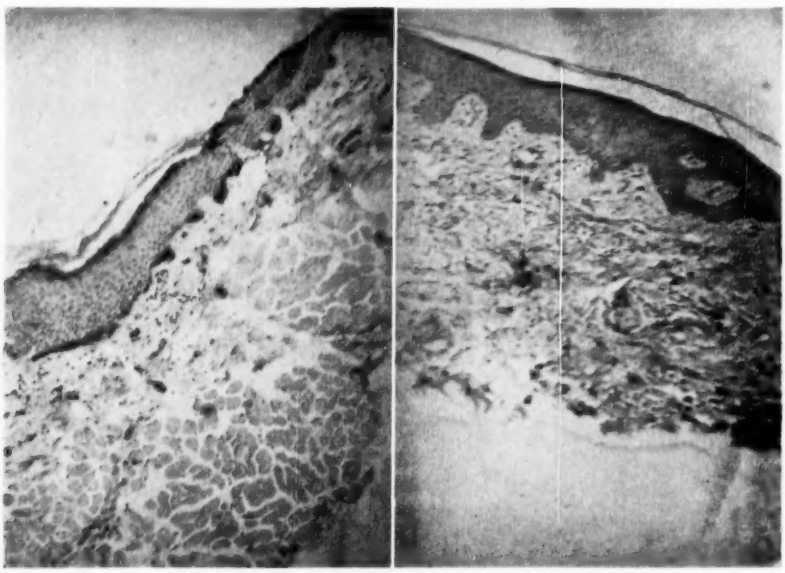

Fig. 2.—Sections from the lower lip of a cretin before and after thyroid therapy.

The corium was increased in thickness, often changing from a state of complete atrophy to one of normalcy. The collagenous connective tissue was denser and greater in amount. On the whole, it no longer showed fragmentation and disorganization; in many cases, it appeared quite normal. Edematous changes within the connective tissue were present only to a very small degree. The extensive degenerative changes of the elastic tissue seen in the earlier sections had been completely rectified.

Sweat glands, hair follicles, and sebaceous glands were increased in numbers; in addition, greater vascularity and cellularity of the dermis were noted in two specimens.

Sections stained with mucicarmine and by the McManus technique revealed no evidence of mucin or mucopolysaccharides in either of the sections taken before or after thyroid therapy.

Sections stained with toluidine blue showed mast cells few to rare before treatment but appearing in larger numbers after thyroid therapy. This seemed, however, to be a reflection on the greater width of the corium rather than an increase in the number of cells per unit area.

SUMMARY

Hypothyroidism developing early in life produces a number of changes of interest to the dermatologist. The cretin presents a cool, dry bronzed or pasty white skin. Disturbances in the amount, texture, and distribution of hair are common, but nail changes are of minor importance.

Cretins tolerate cold poorly and are definitely hyporeactive to cold pressor tests. On the other hand, in such patients, the minimum erythema dose of ultraviolet light is greatly increased. Much less pigmentation develops in cretins following ultraviolet light than in normal controls.

A typical reaction follows the intradermal injection of histamine phosphate although most cretins fail to develop the triple response of Lewis after the firm stroking of the skin. Since sweating is greatly diminished in cretins, variations from the normal occur after the administration of epinephrine, methacholine chloride, and pilocarpine by various routes.

Histologically, there is thinning of the epidermis and corium and scarcity of the cutaneous appendages. Hyperkeratosis, thickness and prominence of the granular layer, and thinning of the stratum mucosum characterize the epidermis. Fragmentation and shattering of the collagen bundles and fibers and striking degeneration of the elastic tissue are noted in the corium. Slight edema is present, but true myxedematous changes were not outstanding.

Many of the clinical and pathologic findings respond promptly to thyroid therapy; however, others apparently involved degenerative changes and are permanent in character.

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ABSTRACT OF DISCUSSION

DR. CLARENCE S. LIVINGOOD, Detroit: As all of you know, we are indebted to Dr. Butterworth for his important observations on the dermatological manifestations associated with neurological disorders of the feebleminded. The paper which he has presented today deals with the changes of the skin, hair, and nails of persons with cretinism. He has recorded certain other data, including the results of cold pressor tests, the effects of ultraviolet light and trauma, and of epinephrine and mecholyl and sweating responses of these patients. The series of cases is large enough to be of statistical significance; the studies of these patients were well planned and carried out in a painstaking manner.

It is obvious that the skin is a very important system for the diagnosis not only of myxedema and hypothyroidism, but also, for certain other endocrine disorders. The same observation applies in regard to the evaluation as well as the possible side-effects of endocrine therapy.

The variation in some of the findings which Dr. Butterworth noted is interesting. For example, although the skin of cretins is usually dry and coarse, 4 of his 14 cases had a normal amount of moisture on the skin. This was one of the manifestations which improved in that after thyroid therapy 6 of the remaining 10 patients developed moisture of the axillae and 3 in the submammary region. In view of the fact that many physicians tend to associate more or less diffuse alopecia with hypothyroidism, it is important to emphasize that only 2 of his 14 patients had definitely sparse hair of the scalp, and 4 had hair of normal texture. Along the same line of thought, it is equally important to note that the nails of all of the patients in this series except one were normal in texture. The response to ultraviolet light exposure which

was noted might be explained by the markedly decreased peripheral and skin blood flow characteristic of myxedema patients. I am wondering if Dr. Butterworth has an explanation for the "bronze" color of six of his patients in contrast to the pasty white or yellowish color of the typical cretin as described in textbooks.

Evidently, the duration of the myxedema or cretinism is the most important factor in the development of tissue changes. The longer the deficiency without treatment, the more extensive the changes and the more difficult to reverse the changes with treatment. The present study concerned the reversal of changes which took place after approximately two months of therapy. I would like to ask Dr. Butterworth to comment on the extent of further improvement in some features of involvement which he would expect after more prolonged therapy.

Dr. Richmond Smith, Chief of the Endocrinology Division of the Henry Ford Hospital, with whom I discussed this paper made the comment that the results of the cold pressor tests which Dr. Butterworth has reported are in line with recent observations that the majority of hypothyroid patients have impaired pressor responses on administration of epinephrine and that the previously abnormal responses are restored toward normal following thyroid therapy. In other words, in a thyroid-deficient person, thyroid hormone appears to potentiate the effect of epinephrine.

Again, I wish to thank Dr. Butterworth for this valuable contribution to the literature on this subject.

Dr. Sture A. M. Johnson, Madison, Wis.: This study by Dr. Butterworth is unique not only in that he was able to collect so many cases, but also in the studies that were performed.

His series and others that I have reviewed do not report a single instance of blonde hair in a cretin. Other organs and tissues of ectodermal origin may show changes. Dentition is abnormal, being retarded, irregular, with a lack of caries and a frequency of paradentosis points.

Neurological findings show diminished hearing and often deafness, as well as decreased or absent knee reflexes. Electroencephalographic tracings in cretins show a decrease in the 10 cycle alpha rhythm. This is increased with thyroxin administration. Atrophic changes of the brain seem to be more marked in the cerebellum, which may account for the disturbed coordination and vertigo, particularly present in the myxedematous patient.

It has been reported that there is retardation in the rate of healing of surgical wounds and ulcers in cretins. I wonder if Dr. Butterworth found this true when he took surgical specimens for biopsy?

Other studies have shown an increased radioactive iodine uptake in the goitrous or epidemic cretin. These individuals do better with iodine than with desiccated thyroid medication. Did Dr. Butterworth do radioactive iodine uptake studies on any of his patients, and, also, did he find thyroid administration precipitated or aggravated a psychosis of any type?

I, too, was interested in the failure of untreated cretins to develop erythema and subsequent pigmentation following ultraviolet therapy. My explanation rather differs from Dr. Livingood's in that I thought probably the hyperkeratosis, thickness and prominence of the granular layer demonstrated by Dr. Butterworth would account for this particular change.

In closing, I wish to thank and to congratulate Dr. Butterworth for an excellent paper.

Dr. Robert L. Gilman, Oakland, Calif.: I should like to elaborate on a larger aspect of Dr. Butterworth's work and its implications.

I have enjoyed, as many of you have, in the past 15 years Dr. Butterworth's contributions to the dermatologic descriptions of this unfortunate group of patients. His interest in this has been unique, and indeed he has become, a specialist within a specialty.

I think the important part of this is that while his work is thoroughly understood and appreciated by dermatologists and is widely quoted and that while he appears in all our textbooks as an authority on these conditions, I do not believe that internal medicine as a group is sufficiently conversant with his contributions. Dr. Butterworth has contributed greatly by his powers of observation and hard work to a better understanding of physical diagnosis in medicine. Other dermatologists might well consider this aspect of internal medicine as a fertile field and in their teaching start interest in dermatology in the second year of medicine.

Dr. Thomas Butterworth, Reading, Pa.: My series of cases was too small to divide into the several groups of sporadic cretins, goitrous cretins, and the childhood myxedema cases.

I think we may say that sweating is more likely to occur in the young sporadic cretins and in the cases of childhood myxedema rather than in the older groups.

With regard to Dr. Livingood's question of the bronzed versus the white skin, I have no explanation for that. In the case reports in the literature, both bronzed and pasty white skins are mentioned, but no percentage incidence of the two types was found. In our cases, they were distributed about half in each color.

As to the subsequent course of these patients (and this will answer Dr. Johnson's question as well) misbehavior was very evident among the older cretins who were treated. One challenged and severely trounced a patient twice her size. Another broke a window. A third insisted on lying on the floor instead of going to bed; thus the older age group became behavior problems. We took them off thyroid entirely or restricted it to ¼ or ½ grain (15 or 30 mg.) a day. We will keep the younger patients on thyroid. They are much more alert and in better physical condition, although, as has been said, the brain damage has been done and anything that we do now will not repair the central nervous system. It is probably well that we do not continue the older patients on what we consider average doses of thyroid, because I do not believe their cardiovascular systems are geared to the higher rate of metabolism that a grain or two of thyroid would give them.

As Dr. Johnson mentioned, the teeth of these patients are remarkably good, particularly in the late 30's and 40's.

About the healing of the wounds, I found a peculiar situation. In the first series of biopsies, which were performed before the administration of thyroid, the wounds healed very promptly, without any infection. After thyroid, the wounds took a much longer time to heal and a number of them became infected, probably because the more agitated patient would pick at them and play with the wound.

We were not equipped to do radioactive iodine studies, but most of these cases had been studied by endocrinologists or internists before their admission, and, perhaps, some of them had had radioiodine studies.

In regard to the absence of a normal response to stroking and ultraviolet light in cretins, it is well to note that the mast cells are decreased in the skins of these individuals and perhaps less histamine is liberated following trauma of various types.

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EXCORIATED ACNE OF YOUNG FEMALES

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BROCQ,[1] in 1898, described this condition minutely, named it, and outlined his treatment. His masterly description has not been improved to this day. In 1915, Adamson [2] drew attention in the English literature to Brocq's work and placed this disease in a classification. In Volume 1 of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY, two papers are devoted to "Neurotic Excoriations." In one, Pusey and Senear [3] discuss Adamson's paper very completely and mention the fact that scant attention has been paid to this subject in the American literature. In the paper by MacKee,[4] Cases 5 and 6 which he presents were probably excoriated acne and not neurotic excoriations, judging from his description of the disease and the excellent response to therapy. Following these papers, there is a paucity of reports on this disease.

Excoriated acne is described in most of the standard dermatological textbooks published in England and America, and some of the descriptions given by the authors and advice regarding treatment are excellent, but little has been added since 1920.

It is my purpose to endeavor to show that excoriated acne of females is more common than is usually supposed, that its lack of recognition often results in inadequate treatment, and that such inadequate treatment causes needless mental upset to the patient and persistence of the eruption for years.

CLASSIFICATION AND CLINICAL DESCRIPTION

The modification by Pusey and Senear of Adamson's classification appears to be the most comprehensive one.

Group I.—Cases in which the self-inflicted lesions are produced surreptitiously (dermatitis artefacta)

Group II.—Cases in which the lesions are self-inflicted through a nervous impulse but without deception being an essential factor in the practice:

(*a*) Neurotic excoriations (Erasmus Wilson) or dug-out excoriations (Colcott Fox)

(*b*) Acne urticata (Kaposi)

(*c*) Excoriated acne of young women (Brocq).

Group I.—Dermatitis artefacta can immediately be dismissed as it has no bearing on the present subject.

Group II.—Neurotic excoriations are usually manifested by elongated deep ulcers or excoriations which result in severe and deep scarring. The lesions are usually in lines most easily produced by a fingernail. They are as common in males

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as in females and may occur anywhere in the body within easy reach of the hands. Frequently they are more numerous on the left side of the body in right-handed persons. These lesions are usually evidence of a deeply fixed neurosis or a psychosis.

Acne urticata, according to Kaposi,[5] is manifested by extremely itchy small hard papules which may appear on the forehead, nose, chin, cheeks, scalp, and later on the extensor surfaces of the extremities. On account of the severe itching, the patient digs and excoriates them.

Adamson believes that the itching is the first symptom; the patient then rubs and produces a wheal or papule, which is then excoriated.

Excoriated acne of young females, according to Brocq's description, is seen in the age group 16 to 24 years. It is most common in pale, rather feeble girls. During an interview, they constantly put their hands to their faces.

On examination the forehead reveals brownish marks of a café au lait shade. There are some crusts and rose-colored excoriations. The lateral aspects of the cheeks may show papulopustules in the parotid area typical of acne vulgaris. Comedos may be distributed over the face.

The patient readily admits spending a considerable time each day opening papules and pustules with a needle or with the fingernail and expressing real or imaginary comedos with such violence that the skin is torn. Brocq states that this becomes a mania. The skin is not itchy, but the patients have a compulsion to dig and pinch which they cannot resist. He further stated that they may stand in front of their mirrors for hours and explore their faces minutely, digging out or expressing imaginary foreign matter and germs.

Adamson's description of this disease substantiates Brocq's, and he further states that the patient is frequently accompanied by an overzealous mother who is sure that her daughter has a grossly disfiguring disease which is ruining her matrimonial prospects. The mother's concern rivets the daughter's attention on her own skin.

There is little to add to these excellent descriptions by two astute observers. However, it has not been my experience that these girls or women are of the pale, feeble type. They may be divided into three groups:

(*a*) Slightly masculine type

(*b*) Vain type of girl who thinks of nothing but her appearance and spends hours each day in front of her mirror

(*c*) Good-looking type of girl who does not have as much attention from the opposite sex as she feels is her due and who blames the real or imaginary blemishes on her face for this lack of attention.

The striking feature of the appearance of the patient's face is that numerous very superficial crusts are present, together with brownish stains and superficial scars. On close examination, there is frequently a complete lack of the typical lesions of acne vulgaris, comedo, papule, and pustule, but there is often increased oiliness of the face.

If these patients are seen repeatedly, one is impressed by the fact that if they are improved no new excoriations or crusts are seen, and in place of these lesions are seen brownish stains and superficial scars. If, however, numerous new excoriations and crusts are seen and the patient is told that she has been picking her face, she will usually readily admit it and state the reason—often school examinations, fatigue, upset at home or office, or with someone of the opposite sex. With continued

improvement, the brownish stains gradually fade and the scars become less prominent. The seasonal exacerbations seen in acne vulgaris are not observed in this disease, but there is often some premenstrual flare as is seen in acne.

ANALYSIS OF PATIENTS WITH EXCORIATED ACNE

An analysis of 12,000 consecutive private patients revealed the following:

Condition	Patients No.	Patients %
Excoriated acne (females)	73	0.6
Excoriated acne (male)	4	0.033
Artefacts (one male and one female)	2	0.016
Neurotic excoriations (male)	17	0.14
Neurotic excoriations (female)	16	0.13

If excoriated acne does occur in the male, it is a very uncommon disease.

Age Incidence.—The age incidence was the following:

Age, Yr.	No. Patients
11 to 20	20
21 to 30	34
31 to 40	19

Of these, the youngest was 16 and the eldest 40 years.

If the age grouping given here is substantiated by other investigators, then the disease should not be called excoriated acne of young girls or young females but excoriated acne of females. The age incidence appears to last from puberty almost to the menopause and in that parallels acne vulgaris.

Occupation.—The occupations of the patients were as follows:

Occupation	No. Patients
1. Office worker	32
2. Housewife	21
3. Student	10
4. Nurse	3
5. Schoolteacher	2
6. Dietitian, Physician, Social worker, Model, Factory worker	1

No conclusions can be drawn from the occupation of the patients except the high percentage of white-collar workers and low percentage of factory workers. It is possible that the former are more critical of their appearance or that the latter have less free time to damage their faces. More white collar workers are private patients, and this fact may entirely account for the difference. It is an uncommon disease in outpatient skin clinics.

Duration of Disease.—The average duration of the condition in the 73 patients was 6.5 years; the shortest duration was three months and the longest 21 years.

Location of Lesions.—Lesions were located in the following areas:

Location	No. Patients
Face only	51
Face and back	15
Face and other parts of body	7

Associated Acne Vulgaris.—Twenty-four patients presented typical lesions of acne vulgaris, oiliness, comedos, papules, and pustules in addition to excoriations, crusts, stains, and scars.

Forty-nine patients presented no lesions of acne vulgaris apart from increased oiliness of the face. On repeated examinations of some of these patients no comedos were observed.

This, in my opinion, is extremely important from the standpoint of diagnosis and treatment. It raises the point as to whether this disease should be called acne, but at present no better name is suggested than the one proposed by Brocq.

Many of these patients without associated acne had been treated as acne vulgaris by their family physicians and some by other dermatologists without any appreciable improvement in their condition.

Results of Treatment.—In 73 patients the following results of treatment were observed:

	Patients	
Results	No.	%
Improved or cleared	36	49
Slightly improved	20	28
Improved and relapsed	3	4
Unchanged	14	19

The good results in this disease are only 50%, even with full knowledge of the condition and all facilities to treat the attendant acne if present. Unless the patient can be persuaded to leave the face alone, failure is bound to occur in exactly the same way that fingernails will not grow in a nail-biter unless the habit is broken.

TREATMENT

The three requisites for treatment of this condition are encouragement, kindness, and firmness in dealing with the patient.

After a careful history and examination, it is essential to take some time to discuss with the patient and her parents her disease, the relationship to acne if present, and the fact that usually 90% of the lesions are produced by her own fingernails. It is necessary to stress the fact that picking produces excoriations and crusting which may result in pigmentation and scarring. All magnifying mirrors must be removed. Too vigorous scrubbing of the face must be avoided, and the patient must be warned that under no condition is she to attempt to express comedos or to open papules or pustules. While reading or studying, she must watch that her hands do not stray to her face.

Any attendant acne vulgaris must be treated vigorously by the dermatologist with the best means at his command.

Sulfur lotions are of value in reducing the increased oiliness so long as they do not produce too much dryness with a resultant increased attention to the face. MacKee used x-ray treatments to advantage in his cases of neurotic excoriations and

the two cases of excoriated acne included in his group. The chief value of x-ray therapy is to improve attendant acne. In addition there may be a psychotherapeutic value in that the patient is impressed that everything is being done that is possible. With a short series of x-ray treatments, the patient is observed frequently and can then be encouraged if she is obeying instructions or cautioned firmly if not.

Although the urge to pick amounts almost to a compulsive obsession, it is doubtful if these patients have any deep psychoneurosis, and for that reason referral to a psychiatrist is of doubtful value. Patients who continue to excoriate their faces notwithstanding the best efforts and advice of a dermatologist might receive benefit from psychiatric consultation. It is doubtful whether the urge to pick represents anything more than a bad habit and not some obsessive compulsion from which they receive masochistic pleasure while excoriating themselves.

With kindness, firmness, and much encouragement, many of these patients can be greatly helped to conquer an extremely stubborn habit.

CONCLUSIONS

1. Excoriated acne of females is seen fairly frequently in private practice.

2. It may be associated with mild acne or seen in patients without attendant acne lesions.

3. It is common up to the age of 40 years and therefore should be called "excoriated acne of females" and the adjective "young" deleted.

4. By treating the attendant acne and by encouragement and firmness in dealing with the habit of picking, many of the patients can be benefited.

ABSTRACT OF DISCUSSION

Dr. Arthur G. Schoch, Dallas, Texas: I find myself in complete agreement with Dr. Wrong's main thesis to the effect that these patients should be treated intensively with all methods at our disposal. I have always regarded, this entity, acné excoriée, as a variant of acne vulgaris, and approach the problem from this standpoint with regard to therapy.

I cannot agree that these patients fall into one of three types; namely, the masculine type, the vain type of individual, or the good-looking young woman who spends too much time at her mirror. Our patients fall into no particular type or category. I must emphatically agree that concomitant typical active lesions with comedones, papules, and pustules are usually conspicuous by their absence, and that a considerable number of these women show little or no apparent spontaneous improvement. In addition, practically all of our experience with acné excoriée is in private practice. It is practically never seen in the charity clinic. In our group, smaller than that of Dr. Wrong's, approximately half in number, only rarely were areas involved other than the face. It is my impression that satisfactory results are forthcoming in a little more than 50%.

I certainly agree that the urge to pick is a bad habit, amounting almost to an obsession, that must be carefully explained and repeatedly discussed and discouraged. I feel, however, that like other bad habits associated with childhood and adolescence, it runs a rather self-limited course over a period of months or several years and disappears just as spontaneously as it appeared.

In a number of instances, the administration of Vitamin B complex by mouth has meant the difference between success and failure; vitamin A's value is questionable.

At the beginning of treatment, I almost invariably make rash promises of cure to each individual, knowing full well that there will be an appreciable failure rate. At this particular time I also try to focus the attention of the patient on a period of at least six months and possibly a year hence when they should look for marked improvement or complete relief, stressing the

fact that even preliminary improvement within a few weeks is out of the question. I routinely include a course of superficial x-ray therapy, usually giving the treatments at biweekly intervals instead of weekly intervals. We never exceed a total dosage of 600 r.

I believe that when, as a result of treatment, acne papules cease to make their appearance, most of these patients lose their incentive to pick at their skin, and I invariably make this statement to the patient and repeat it at frequent intervals.

I think the subject is important and that Dr. Wrong has presented it well. I believe that this method of treatment is the best available today and that his therapeutic results err slightly on the side of conservatism.

Dr. Herbert S. Alden, Atlanta, Ga.: Of course, it is always enlightening to examine old concepts within the scope of our expanding experience, and I think we should be appreciative of this presentation by Dr. Wrong on excoriated acne in young females since it brings to our attention one of the smaller things, really the bread and butter of dermatology. More often than not, you know, we dermatologists deal in the "little things" in medicine, those little things which often prick our therapeutic pomposity.

Socially and economically, we have come a long way since the original description of this clinical concept, and I think it safe to say that the "chlorotic" young female of the early 1900's, with her pale cheeks, stringy hair, flat chest, and cotton stockings, now wears rouge and powder, if not a Florida suntan, has a permanent wave hair-do, belongs to a sorority, wears "falsies," and sheer nylon stockings. I think often she is far to busy with her social and school activities to be sitting home, picking her face in frustration.

In fact, I don't see as many patients with excoriated acne as Dr. Wrong seems to have seen, but in spite of this change in customs, we still have an acne which is excoriated. But, like Dr. Wrong, I think the terms, "young" and "female" are no longer necessary, for in my experience the condition is confined neither to youth nor to the female. It is the result of manifold social, family, or economic fears, and as such often becomes a fixed obsession which no amount of psychiatric care seems to change. However, I am impressed by the fact that often a clear explanation and, if possible, a challenge—that is, challenging the patients to do better—plus a diversion of attention—works wonders. If you can tell them how pretty their eyes are or how much better looking they are on profile, and divert their attention, many times this turns the trick.

Dr. James Lewis Pipkin, San Antonio, Texas: In addition to the therapeutic suggestions considered, a few other practical points might be worthy of mention.

As a rule, this "picker's" complex is found in very nervous, tense individuals. We have found that repeated small doses of a mild sedative will often break this vicious cycle; for example, a small dose of phenobarbital for a few weeks seems to be very helpful. The institution of some very decisive means of breaking this vicious picking habit, such as advising the wearing of light cotton gloves at night when the patient is reading or studying, is helpful. If this fails, tying on light-weight boxing gloves will at times prove helpful. In other instances, cautioning patients and forbidding them to look at their faces in the mirror, searching for blemishes, and ordering them upon arising in the morning immediately to cover the face with some make-up base to prevent the "eyeing" of the lesions, are worth-while suggestions.

Dr. Stephen Rothman, Chicago: I wonder if all these cases represent true excoriated acne or whether some of them are simple neurotic excoriations. Many patients with neurotic excoriations claim that they dig because they have acne lesions, but they are never able to show a nonexcoriated "primary" lesion. The material presented includes women up to the age of 40. True acne in this age group must be very rare if it exists at all. I grant that neurotic excoriations can be a manifestation of deep-seated conflicts or even of psychoses, but there are many cases in which the digging is just a bad habit. The habit can be successfully combated by skillful handling of the patient and by administering some sedatives.

Dr. Harry J. Templeton, Oakland, Calif.: I hope I am not wasting your time by reminding you that a simple yet practical approach to this problem is to have the patient cut her fingernails back to the quick.

Dr. Norman M. Wrong: I agree with Dr. Schoch that this condition often has a self-limited course, that we see these youngsters frequently from the age of 15 to 18 with this disease, and apparently it is a habit which stops spontaneously and they get better.

I have not tried vitamin B. I agree with him that small doses of x-ray—and I certainly rarely exceed 60 r—are helpful. I think that a good part of the value is that you are seeing the patient repeatedly and giving her lots of encouragement.

In reply to Dr. Alden, I agree with him that a clear explanation and a challenge to these patients is important and that the most difficult person to deal with is often the mother.

Dr. Pipkin's suggestion of phenobarbital is well worth a trial, and also urging the patient to wear gloves. I believe, however, that some of these people pick at themselves with forceps or occasionally with a needle, so that the wearing of gloves doesn't entirely eliminate the difficulty. To cut their fingernails closely is certainly of value.

In reply to Dr. Rothman, there is no sharp line between excoriated acne and neurotic excoriation. I believe in my series I have included some cases that other people would call neurotic excoriations. However, if we go back to Erasmus Wilson's description, he stressed the fact that in neurotic excoriations there are deep, linear ulcers, whereas in the cases that I have shown there are very superficial ulcers and crusts which heal with a very superficial scar. This certainly does not fit into Erasmus Wilson's original description of neurotic excoriations.

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CUTANEOUS LYMPHOBLASTOMA

Report of Two Unusual Cases of Reticulum Cell Sarcoma with Emphasis on Cutaneous Touch Smears

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THE VALUE of cutaneous touch smears as a diagnostic aid has been emphasized in several studies.* We wish to report two unusual cases of lymphoblastoma that demonstrate the value of this procedure in establishing the correct diagnosis.

REPORT OF CASES

CASE 1.—A 33-year-old white man was first seen at the Mayo Clinic in April, 1949. In November, 1948, nodular lesions had appeared over the sternum; these gradually became generalized, but spared the scalp, face, palms, and soles. No local or systemic symptoms were noted. Physical examination revealed a generalized cutaneous eruption consisting of discrete fawn-colored to red papules and nodules ranging from 1 to 10 mm. in diameter (Fig. 1*a*). The axillary and inguinal lymph nodes were palpable, and hypertrophy of the pharyngeal lymphoid tissue was present.

Cutaneous biopsy from the abdomen revealed reticulum cell sarcoma, and touch smears made from the surface of the biopsy specimen revealed immature reticuloendothelial cells (Fig. 2). Urinalysis showed nothing abnormal. Results of quantitative studies of the blood were normal. Examination of smears of peripheral blood revealed an occasional monocyte with reticuloendothelial characteristics. Study of sternal bone marrow showed slight increase in monocytes and eosinophiles. A roentgenogram of the thorax disclosed bilateral soft infiltration in the apices and infraclavicular portions of the lung suggesting active tuberculosis.

The patient was given intravenous injections of nitrogen mustard in doses of 0.15 mg. per kilogram of body weight on two successive days, with pyridoxine. Within two weeks the skin nodules were flattened until only pigmented macules were evident. Cultures of sputum and gastric contents gave no evidence for tuberculosis, but roentgenograms showed an increase in the lesion in the apex of the right lung.

The patient returned in July, 1949. He stated that six weeks previously (two months after he received mustard) he had cutaneous lesions at new sites, although the old lesions were still quiescent. The new lesions consisted of many small (2 to 4 mm.) flesh-colored firm nodules; some were discrete, whereas others were confluent. They occurred over the back, thorax, and arms. Noninfiltrated brown macules also were present. Results of laboratory examinations and thoracic roentgenography were unchanged. The patient was given a total dose of 0.4 mg. of nitrogen mustard per kilogram, and the nodules cleared rapidly.

Fellow in Dermatology and Syphilology, Mayo Foundation (Dr. Feldaker) and Section of Dermatology and Syphilology, Mayo Clinic and Mayo Foundation, (Drs. Kierland and Montgomery); the Mayo Foundation is a part of the Graduate School of the University of Minnesota.

* References 1 through 6.

He returned in January, 1949, because of recurrence of nodules. Nitrogen mustard again gave improvement when used in the same dose.

The patient returned in May, 1950, because of the development of new nodules for two and one-half months. Cutaneous biopsy revealed the same findings as before. Submental, axillary, inguinal, and left epitrochlear lymph nodes were palpable. The patient received roentgen therapy to the involved areas at this time. By July, 1950, the lesions had cleared more nearly completely and rapidly than with any prior therapy. Further roentgen therapy was given in September,

Fig. 1 (Case 1).—Reticulum cell sarcoma: (*a*) Generalized discrete nodular eruption in April, 1949; (*b*) Clearing of eruption after treatment (August, 1951).

1950, because cutaneous lesions were again prominent in areas where the irradiation had been minimal.

By February, 1951, many new cutaneous nodules had developed and the patient complained of nocturnal cough and loss of weight. Thoracic roentgenograms revealed diffuse opacity of the upper two-thirds of the left lung and progression of the process in the right lung. The patient received roentgen therapy over the lungs. By March, 1951, he was much better. He had regained weight, and the cutaneous nodules had subsided even in regions not exposed to roentgen therapy. Involvement of the right upper lobe was less pronounced but there still was consolidation in the left upper lobe.

In August, 1951, the patient returned because of increasing diarrhea for two months, manifested by three to five stools daily and intermittent cramping abdominal pain. Cutaneous nodules had been minimal but were recurring. Severe nonproductive cough was associated with mild dyspnea. Physical examination revealed some pale-red nodules primarily on the face, but the remainder of the skin was clear (Fig. 1*b*). Fine rales were audible over the thorax on the

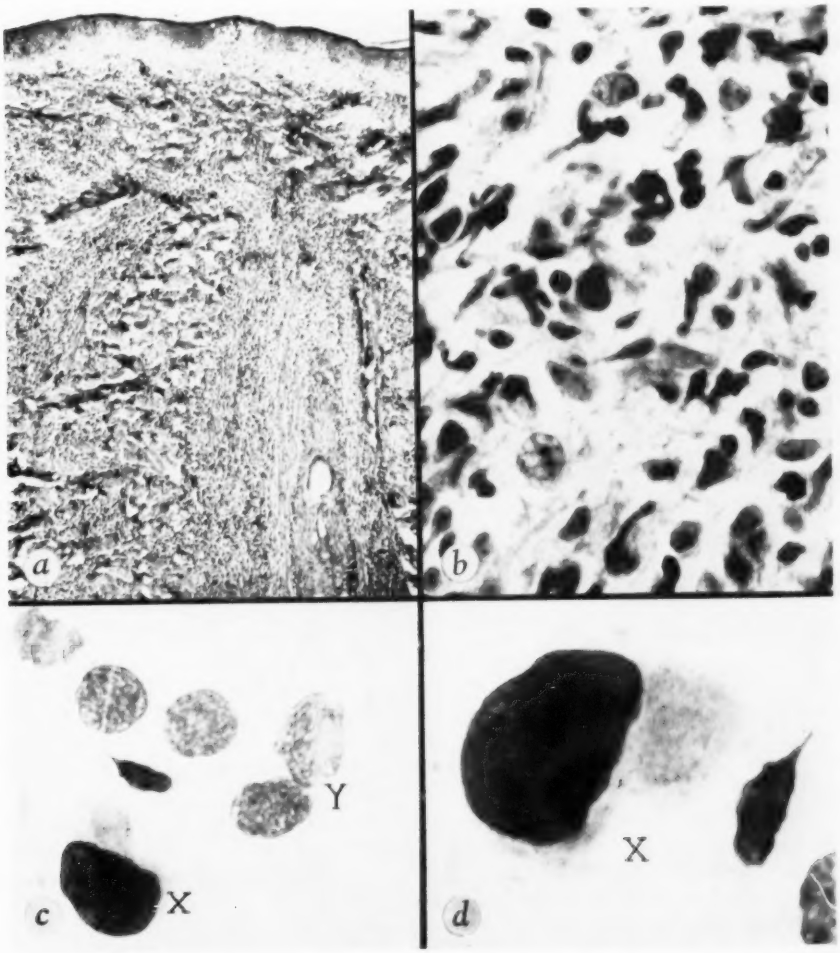

Fig. 2 (Case 1).—(*a*) Paraffin section of skin from abdomen showing reticulum cell sarcoma (hematoxylin and eosin; × 50); (*b*) Paraffin section. Note dark-staining immature reticulum cells and mitotic figures; (hematoxylin and eosin; × 900). (*c*) Cutaneous smear; immature reticulum cell at *X*; large nucleus in relation to cytoplasm; dark reticulated nucleoplasm. Cells at *Y* are normal histiocytes (Wright's stain; × 900). (*d*) Cutaneous smear. Same reticulum cell at *X* at higher magnification (Wright's stain; × 1,700).

left, and mild ankle edema was noted. Hematologic studies again showed no abnormalities. Stools were negative for parasites. Results of proctoscopy and colonic roentgenography were normal. The value for total serum protein was 4.33 gm. per 100 cc.; the albumin was 2.98 gm.,

and the globulin 1.35. Roentgenograms of the small intestine showed flattening of the mucosal folds, particularly in the jejunum. The loops were separated as if by a thickening of the intestinal wall, possibly the peritoneal coat. The roentgenologist suggested the presence of a diffuse inflammatory or neoplastic peritonitis. A roentgenogram of the thorax showed considerable resolution of the consolidation in the left upper lobe with diffuse fibrosis in both lungs.

These findings suggested that the pulmonary lesions were a part of the "reticuloendotheliosis"† and that the diarrhea could be explained by lymphoblastomatous infiltration of the intestine. Roentgen therapy over the abdomen produced improvement with regard to the diarrhea.

The patient was again seen in September, 1951, because of an enlarging mass on the right side of the neck of two weeks' duration, associated with fever and loss of weight. Physical examination revealed a temperature of 100.2 F., clubbing of the fingers, and indurated masses on the right side of the neck and over the left mandible. Enlarged lymph nodes were palpable in the left supraclavicular and axillary regions. The patient received roentgen treatment. When he returned one month later, the masses were gone. Because some of the thoracic lesions showed increasing activity, the patient was given another course of roentgen therapy.

The patient returned home, and died in January, 1952. Through the courtesy of Dr. R. W. Ramlow, LaCrosse, Wis., we received a final report of the patient's course and specimens removed at necropsy. The microscopic slides were examined by Dr. W. A. Bennett, of the Mayo Clinic; he reported infiltration of lymphoblastomatous reticuloendothelial cells in the lungs, stomach, large intestine, spleen, bone marrow, liver, lymph nodes, and pancreas.

CASE 2.—A 50-year-old white man was first seen at the clinic in January, 1948. In July, 1947, pruritic cutaneous nodules had developed over the buttocks; this eruption subsequently became generalized. The patient's general health was good. Physical examination revealed a generalized papulonodular eruption sparing the palms and soles (Fig. 3*a*). Single and confluent red nodules ranging from a few millimeters to 1.5 cm. in diameter were superficially situated in the cutis and subcutaneous tissue. Axillary, inguinal, and epitrochlear lymph nodes were palpable. The tonsils were large and cryptic, and the liver was palpable 2 cm. below the right costal margin. Slight pitting edema of the legs was noted.

Biopsy of skin from the forearm and lumbar regions showed reticulum cell sarcoma. Touch smears from the cut surfaces of the biopsy specimens showed immature reticuloendothelial cells (Fig. 4). Routine studies of the urine and blood showed no abnormalities. A differential count of blood cells showed 9.5% monocytes. The erythrocytic sedimentation rate was 34 mm. in the first hour (Westergren method). Examination of sternal marrow revealed an increase in monocytes but was not diagnostic. A roentgenogram of the thorax showed nodular and fibrous tuberculosis of both upper lobes; all subsequent films showed no changes. Cultures and inoculation into guinea pigs of gastric contents and sputum failed to disclose Mycobacterium tuberculosis.

The patient received intravenous injections of nitrogen mustard in doses of 0.1 mg. per kilogram of body weight daily for four days, with pyridoxine. Within two and one-half weeks the nodules were softened, brownish, and less infiltrated. Biopsy of skin from the back revealed involution and shriveling of the lymphoblastomatous cells.

When the patient returned in May, 1948, only remnants of the lesions and some pigmentation were evident (Fig. 3*b*). Biopsy of skin from the same area of the back disclosed no evidence of lymphoblastoma.

On his return in July, 1948, the patient stated that he had noted recurrence of nodules for two weeks but he felt well. Cutaneous biopsy again revealed lymphoblastoma. Results of physical examination and laboratory studies were essentially the same. The patient received another course of mustard totaling 0.4 mg. per kilogram. No response to this treatment was evident, and the patient was given roentgen therapy elsewhere.

† This is used in a broad sense, referring to a type of lymphoblastoma defined differently by pathologists and hemocytologists.

The patient returned in September, 1948. Only slight improvement had occurred in the cutaneous lesions. Laboratory examination revealed anemia and leucopenia. A differential leucocyte count disclosed 31% monocytes, 21% lymphocytes, 46% neutrophiles and 2% eosinophiles. The monocytes showed reticuloendothelial characteristics. The patient received superficial roentgen therapy to the body, excluding the face, with moderate improvement.

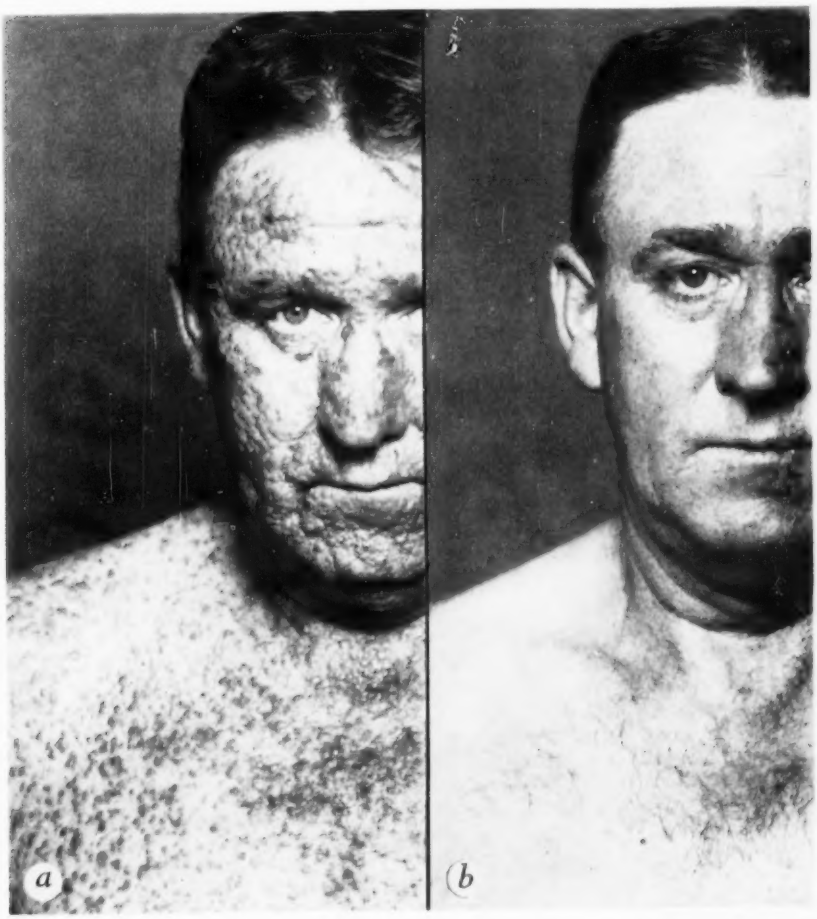

Fig. 3 (Case 2).—Reticulum cell sarcoma. (*a*) Generalized discrete nodules, January, 1948. Note similarity to eruption in Case 1. (*b*) Resolution of eruption after treatment (May, 1948).

In April, 1949, he returned in good health except for some recurrence of nodules on the upper part of the trunk, upper extremities, and neck; these areas were studded with firm, flesh-colored nodules varying from 1 to 3 mm. in diameter. He received superficial roentgen therapy to the involved regions.

The patient was seen for the last time in June, 1949. He reported that the cutaneous nodules recurred and gradually became worse one month after the last course of roentgen therapy. He was unable to stay for further treatment.

In reply to an inquiry in January, 1951, he wrote that his skin was somewhat better. Further inquiries were unanswered, and it was finally learned that he had died in January, 1953. A letter from his wife in March, 1953, disclosed that severe cough, thoracic pain, dyspnea, "asthma," weakness and, terminally, periods of loss of consciousness had developed.

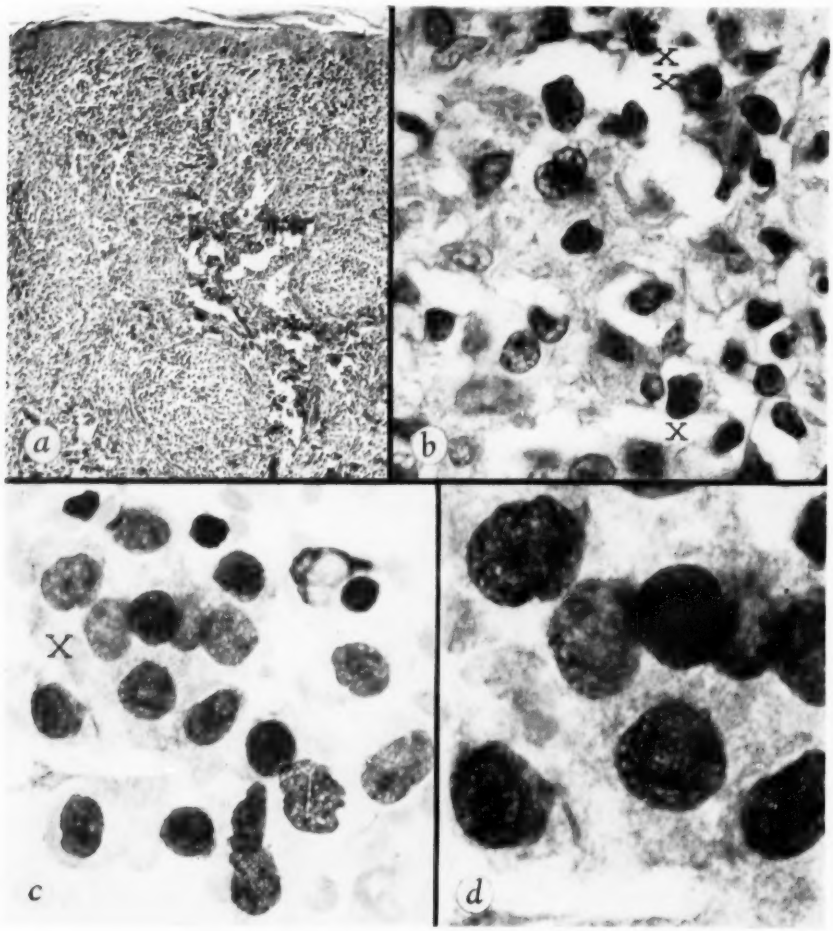

Fig. 4 (Case 2).—(*a*) Paraffin section of skin from forearm showing reticulum cell sarcoma (hematoxylin and eosin; ×90); (*b*) Paraffin section. Note immature reticulum cells and mitotic figures at *X* (hematoxylin and eosin; ×900). (*c*) Cutaneous smear. Group of immature reticulum cells at *X* (Wright's stain; ×900). (*d*) Cutaneous smear; immature reticulum cells. Note large nuclei, fine reticulated nucleoplasm, multiple nucleoli (Wright's stain; ×1,700).

COMMENT

These two patients showed similar cutaneous eruptions consisting of generalized discrete nodules. This is unusual in lymphoblastoma. Nitrogen mustard was of definite value in the production of temporary remissions. In the second patient, cutaneous biopsy at a former site of lymphoblastoma revealed no malignant cells

after intravenous injections of nitrogen mustard. The cutaneous and visceral lesions responded well to roentgen therapy. In the first patient, cutaneous lesions in non-irradiated sites underwent involution after roentgen treatment to the involved regions of skin.

Examination of the peripheral blood and sternal marrow in each patient was not diagnostic. However, smears from the specimen of skin removed for biopsy revealed distinctly immature cells. This confirmed the findings in paraffin sections. It is the impression of one of us (Montgomery) that biopsy touch smears will establish the type of lesion in about 25% of cases of cutaneous lymphoblastoma.

Technic of Cutaneous Touch Smears.—This procedure is simple. The specimen may be removed by excision or cutaneous punch; usually a 4-mm. or 5-mm. punch is adequate. The specimen is cut in half in a plane perpendicular to the epidermis through the suspected area of involvement. Clean scissors or a scalpel is used to divide the specimen. One part of the specimen is used in the preparation of touch smears; the other portion can be used likewise or put into fixative for paraffin sections. In the preparation of touch smears, the cut surface of the specimen is pressed against a clean glass slide to form an imprint; then the specimen is touched to an adjacent part of the slide and a smear is made along the length of the slide. Two or three similar rows are adequate, but several slides should be made as is done in routine hemocytologic studies. The slides are dried by waving them in the air. They are stained by Wright's or Giemsa's method. Special stains can be used as necessary.

SUMMARY AND CONCLUSIONS

Two unusual cases of lymphoblastoma are presented, and the value of the cutaneous touch smear in making this diagnosis is emphasized. The peripheral blood smear in some cases of lymphoblastoma may not be diagnostic, whereas touch smears from the skin may be diagnostic, revealing a few or many immature cells or even blast (stem) cells. The ease in securing these imprints, the distinct cellular structure that they demonstrate, and the reliability of the method should make this technique a routine procedure in any suspected case of cutaneous lymphoblastoma.

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BENIGN CALCIFYING EPITHELIOMA OF THE SKIN

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BENIGN calcifying epithelioma of the skin is rarely diagnosed clinically. No doubt this is due to the general lack of familiarity with this uncommon condition. This is understandable, as most of the contributions to the medical literature have been found in European journals. Furthermore, these European reports have dealt chiefly with the pathological aspects rather than the clinical features of the lesion. A recent notable contribution to the American literature is that of Lever and Griesemer[18] in 1949.

It is the purpose of this paper to add three cases of benign calcifying epithelioma to the American literature, and to add other additional cases to the world literature. Additionally, certain clinical features of this uncommonly encountered lesion which may be of value in its diagnosis and treatment are stressed.

In an institution such as the American Oncologic Hospital, which is devoted to the treatment of cancer and allied diseases, many skin cancers are seen. From 1940 to 1951, approximately 1,600 epidermoid carcinomas of the skin of the head and neck have been treated. During the same period, only three cases of benign calcifying epithelioma have been seen. Curiously, they were all observed recently, within a period of five months.

REPORT OF CASES

CASE I.—M. M., a 58-year-old white woman, first noted a nodule in the occipital region of the scalp six years prior to admission (1944), while in a beauty parlor. Except to arrange her hair to conceal it, she gave no attention whatever to the lesion. Not until one month prior to admission did she consult a physician. After an unsuccessful attempt to excise the large lesion, the physician contented himself with a biopsy. The patient was then referred to one of us (S. G. C.) with a microscopic diagnosis of epidermoid carcinoma, squamous cell type, Grade I.

At this time, on May 1, 1950, an ulcerated mass measuring 7.5 cm. in diameter and elevated 4.5 cm. presented in the occipital area (Fig. 1). The surface was nodular and firm, and the edges were rolled and hard. The lesion seemed fixed to the pericranium. Because our pathologist noted certain unusual microscopic features in the slide sent in by the referring physician, a second biopsy was requested and performed. The second biopsy revealed the lesion to be a benign calcifying epithelioma.

On May 4, 1950, the tumor was widely excised. In depth the specimen included the full thickness of the scalp down to and including the pericranium. Immediate plastic repair was

From the American Oncologic Hospital, (Dr. Castigliano, Chief, Head and Neck Service) and the National Cancer Institute, (Dr. Rominger, formerly Trainee).

Fig. 1 (Case 1).—A large ulcerated, nodular lesion presented in the occipital area. The lesion measured 7.5 cm. in diameter and had been present for six years.

Fig. 2 (Case 1).—Cross section of the gross fixed specimen. The lesion is definitely circumscribed but apparently not encapsulated. The surface made by cutting revealed that the entire central portion is made up of peculiarly lobulated islands of white tissue distributed in a matrix of soft yellowish material. The large masses are made up of mature squamous cells as seen microscopically.

performed with a sliding type of scalp flap. A split-thickness skin graft was obtained from the thigh and applied to the pericranium of the donor site of the sliding graft. An occipital lymph node dissection was also performed.

The patient's wound healed per primam, and the free graft to the donor site showed a 95% take. She was discharged from the hospital on the 20th postoperative day. To date there has been no evidence of recurrence.

The pathological report is as follows: Grossly the fixed "contracted" specimen consists of a large, irregular roughly hemispheric mass of tissue measuring 9.0 by 6.8 by 4.0 cm. in its greatest dimensions. It is partially covered with hairy scalp, which in several areas is ulcerated. The base of the tissue is fibromuscular. The consistency of the entire mass is hard, but it cuts rather easily. The surfaces made by cutting present white irregular islands of tissue in a matrix of soft yellow tissue (Fig. 2).

Microscopic examination shows uniform masses of mature squamous cells (Fig. 3). Some of the cell masses are present deep in the dermis, simulating invasion. Other cell masses are

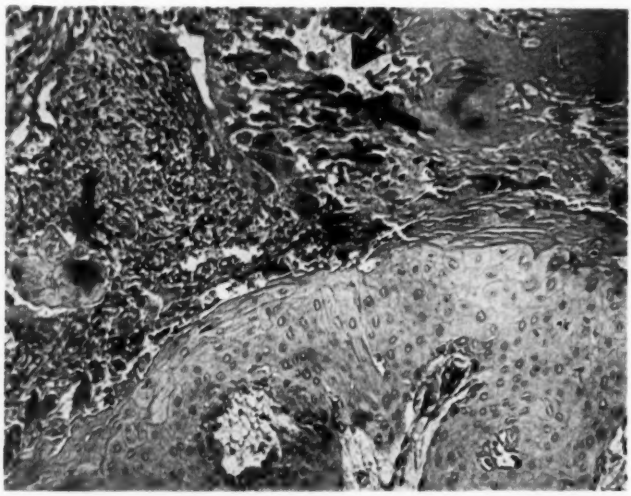

Fig. 3 (Case 1).—Photomicrograph of the lesion. Note the large masses of benign-appearing squamous cells. Calcium salt deposition and foreign body giant cells are visible (arrows).

surrounded by foreign-body giant cells. Few mitotic figures are seen. Numerous areas of calcium salt deposition are noted. Necrosis is present but is not a prominent feature. The pathologic diagnosis is benign calcifying epithelioma.

Case 2.—B. L., a 19-year-old white woman, first noted a painless swelling in the left parotid area 18 months before admission to the American Oncologic Hospital. The swelling gradually increased in size. Seven months prior to admission she visited a physician, who told her it was a cyst but advised no treatment.

When first seen by us, on Sept. 18, 1950, she presented a hard, lobulated subcutaneous mass in the right parotid area which measured 2.4 by 2.3 cm. This was partially fixed to the subcutaneous tissue but not to the parotid gland.

On Oct. 3, 1950, the lesion was completely excised. A gross diagnosis of benign calcifying epithelioma was made at the time of operation.

The wound healed per primam, and the patient was discharged on the sixth postoperative day. To date there has been no evidence of recurrence.

The pathological report is as follows: Grossly the fixed specimen is an ovoid, yellow, soft mass, which measures 2.4 by 2.3 cm. It is surrounded by a thin membranous cyst wall. The

specimen cuts with ease but with a gritty sensation. The surfaces made by cutting in some areas are firm and yellow. In other areas soft greasy material is present.

Microscopic examination shows masses of mature squamous cells surrounded by foreign-body giant cells. Necrosis is a prominent feature (Fig. 4). In many areas calcium salt deposition is noted. The pathological diagnosis is benign calcifying epithelioma.

CASE 3.—A. R., a 72-year-old white woman, first noted a small painless pimple-like lesion on the scalp one year prior to admission. The lesion gradually increased in size. She completely neglected the lesion until three months prior to admission. At that time, she consulted in succession three physicians, each of whom told her not to worry about the lesion. Not satisfied, the patient consulted a fourth physician, who referred her for treatment because of a clinical suspicion of squamous cell carcinoma.

When she was first seen by us on July 31, 1950, a mottled bluish-red and yellow, firm mass, which measured 2.4 by 1.8 by 0.9 cm., presented at the vertex of the scalp. This was

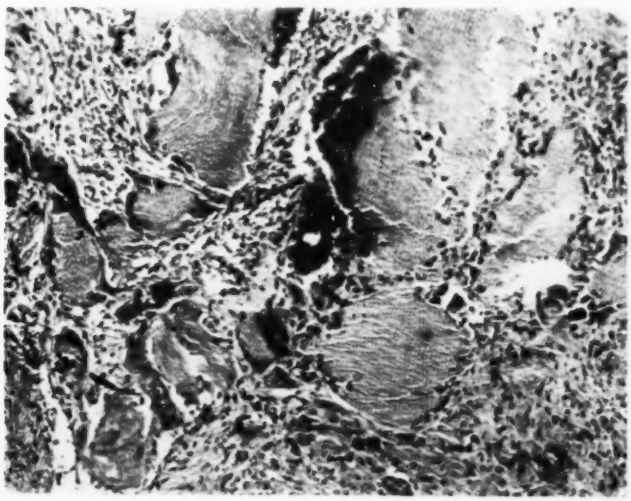

Fig. 4 (Case 2).—Photomicrograph of lesion. Necrosis, calcium salt deposition, and foreign-body giant cells are prominent features.

fixed to the skin and subcutaneous tissue but not to the pericranium. Benign calcifying epithelioma was considered in the differential diagnosis.

On Aug. 2, 1950, the lesion was excised, including 1 cm. of grossly normal skin. The resulting wound was closed by direct approximation. A gross diagnosis of benign calcifying epithelioma was made at the time of operation.

There was some delay in healing, but the wound finally healed after six weeks. To date there has been no evidence of recurrence.

The pathological report is as follows: Grossly the fixed "contracted" specimen consists of an irregular mass of tissue measuring 4.0 by 3.5 cm. It is partially covered with hairy scalp. Several areas are ulcerated. The base of the tissue is fibromuscular. The consistency of the mass is firm, but it cuts rather easily, although with a gritty sensation. The surfaces made by cutting are made up of islands of whitish tissue in a yellow matrix.

Microscopic examination shows numerous islands of mature squamous cells surrounded by foreign-body giant cells and areas of calcium salt deposition. Necrosis is not present. No definite capsule is seen, nor is there evidence of invasion. The pathologic diagnosis is benign calcifying epithelioma.

INCIDENCE

Benign calcifying epithelioma of the skin has been recognized as an unusual pathologic entity for many years. The lesion was named by Malherbe and Chenantais [21] in 1880.

The American literature dealing with the subject is meager. Quite in contrast, the European literature is relatively extensive. It would indeed appear that benign calcifying epithelioma is an uncommonly encountered lesion. Ch'in,[6] in his excellent contribution in 1933, was able to collect only 116 cases, dating back to 1880, and he reports 19 of his own. Côté,[8] in 1936, was able to add 12 cases.

Since 1936 we have been able to find 15 papers dealing with benign calcifying epithelioma in the world literature. Févre,* in 1938, reported five cases, and Highman and Ogden,[15] in 1944, reported 12 cases. King,[17] in 1947, reported 9 cases and Setala,[29] in 1948 reported 29 cases. Scattered reports of 1 or 2 cases each have been published in the South American Literature, adding an additional 13 cases.†

Puente Duany,[28] in 1950, reported five cases. Five cases of multiple lesions have been reported.

Warvi and Gates,[31] in 1943, in a paper dealing with epithelial cysts and cystic tumors of the skin, mention 12 cases in which calcification is a feature but do not specifically state whether or not they conform to the description of benign calcifying epithelioma.

Excluding these last-mentioned cases of Warvi and Gates,[31] we have been able to add 117 reported cases to the 126 collected and reported by Ch'in,[6] in 1933. Puente believed that up to 1950 about 150 to 200 cases had been reported. Thus a total of 243 cases were reported from 1880 to 1950, or nearly 50 more than estimated by Puente.

In a collection of 75,673 consecutive surgical specimens from several hospitals, a total of 36 cases of benign calcifying epithelioma was found. One, then, can expect to encounter one case of benign calcifying epithelioma in about 2,000 surgical specimens. This suggests that many lesions which are removed are either not reported or incorrectly interpreted.

Since 1933, twice as many cases have been reported per year as were reported prior to this time. This increased rate would suggest an increasing familiarity with the lesion.

It is possible that in a significant number of instances these lesions go unrecognized. Lesions clinically diagnosed as sebaceous cysts are too often excised without the benefit of pathologic examination. Some of these lesions, so removed and discarded, may actually be benign calcifying epithelioma.

AGE INCIDENCE

Benign calcifying epithelioma has been reported as occurring at all ages. The oldest patient reported was 80 (Setala [29]) and the youngest, three months (Finkert, cited by Ch'in [6]). Our patients were aged 19, 58, and 72 years.

Approximately 50% of patients are under 25 years of age.[27] Few cases are encountered past age 60; in fact, less than 5% of reported cases. These few have been found in women.[27]

* References 10 and 11.

† References 7, 13, 16, 22, 23, 26, and 34.

SEX INCIDENCE

The average sex incidence has been about equal. However, Malherbe's [19] series showed a preponderence of females. All of our patients were females. Some writers have suggested that perhaps the cosmetic liability of the lesion may have induced more females to seek medical advice. Quite in contrast to this opinion, is Case 1 of our series. The patient, a woman, arranged her hair in such a way as to conceal the lesion for six years. Only when the size of the lesion, through continual growth, made further concealment impossible did the patient seek professional advice. We agree, however, that females in general present themselves earlier, bearing smaller skin lesions than do the males.

SITE INCIDENCE

Most of these lesions have been found about the head and neck. In Côté's [8] series, for example, five were on the face, two each on the neck and arms, and one each on the chest and thigh. In our series all three cases involved the head.

A summary of cases collected and reported by Févre and others [11] in 1938, Setala [29] in 1948, Puente in 1950, and by us in 1953, reveals that the head and neck are involved in about 70% of cases. The upper extremeties are more frequently involved than the trunk. About 80% of all lesions involve the head and neck, upper extremities, scapular and infraclavicular regions.

GROWTH RATE

The lesions have a relatively slow growth rate. The duration of our three cases was one year, 18 months, and six years, and the diameters 2.4 cm., 2.4 cm., and 7.5 cm., respectively. The duration of Côte's [8] cases varied from three to seven years, and the size ranged from that of a pea to the size of a hen's egg. Wilckens [32] (1858) reported a case of 13 years' duration. Perrot (1928) reported a case of 30 years' duration. Puente states that 25% of cases reveal a history of three to six months' duration of the lesion, while another 20% have a growth history of one year. The majority of cases of longer duration seldom give a history longer than 24 months. The growth rate is definitely slower than that of squamous cell carcinoma and basal cell carcinoma as shown by one of us (S. G. C.[5]).

These lesions of slow growth seldom grow to a size larger than a walnut. Larger lesions are occasionally encountered—for example, Case 1 in the series here reported.

PATHOLOGIC CONSIDERATIONS

Grossly, the lesion nearly always is a subcutaneous, yellow or gray, globular, firm or hard mass. In the absence of calcareous deposits or ossification, the lesion may be soft and fleshy. The epidermis is usually intact. As the lesion progresses, it may become attached to the epidermis. In some cases, particularly in larger lesions, the skin surface may be ulcerated, as in Case 1 and Case 2 of our series. Grossly, the lesion when ulcerated may somewhat resemble squamous cell carcinoma of the skin. The lesion cuts easily but with a gritty sensation. The surfaces made by cutting present a mottled grayish opaque appearance with interspersed yellowish cheesy material and islands of grayish solid tissue. A thin or incomplete capsule may be seen.

Microscopically, the lesion is usually encapsulated, and trabeculations are apparent. Many islands or sheets of mature squamous cells are seen. Some of these are viable and others are necrotic. These cells have a strong tendency toward keratinization. These keratinized islands of cells are mummified and take the eosin stain. Hyalinization is encountered in the lesions of longer duration as the keratin undergoes degeneration. The final stage is reached when the hyalinized tissue is infiltrated with calcium salts. Calcification then can be expected to be encountered only in the older tumors. A variable amount of vascular fibrous tissue stroma is seen. Foreign-body giant cell reaction is present in variable degrees and is more abundant in and about the keratinized areas. It is believed that the giant cell reaction is a cellular effort to destroy the keratinizing colonies. The dermis is usually not involved, but in Case 1 of our series the mature islands of benign-appearing squamous cells extended into the dermis and simulated invasion.

On occasion in older tumors actual bone formation is seen, but this is rare. Nicholson,[25] in 1927, described such a case. He believes that the bone is formed by differentiation rather than metaplasia. Other writers disagree with this theory. In any case, the argument is pure pedantry.

Puente believes that there are three distinct types of calcifying epithelioma. The first and by far the commonest is the one above described. A second type is one in which keratinization occurs en masse, giving the lesion a microscopic appearance of mummification. The third and uncommonly encountered clinical variety is associated with cystic degeneration. These cystic lesions contain fluid.

There is some difference of opinion as to the cell type of the lesion. Côté [8] believes the lesion to be basal cell in type, while Nicholson [25] considers the tumor to be squamous cell in type.

Févre ‡ and Setala [29] have advanced the theory that the lesion may spring from the hair follicles. Puente states the lesions begin in the dermis around the hair follicles. In our series, despite the basophilic staining propensities, we believe the lesion in each instance to be squamous cell in type.

MALIGNANCY OR BENIGNANCY OF THE LESION

There is also some difference of opinion as to whether the lesion is malignant or not—e. g., Côté [8] found no evidence of carcinomatous change, while Nicholson [25] believed his case to be an ossifying squamous cell carcinoma. Frey [12] believed these lesions to represent calcified basal cell carcinomas. Strassburg [30] and Bilke considered them to be a type of carcinoma. Malherbe,§ himself thought the lesion to be a benign one but one of his cases recurred four times. Setala [29] believed that one of his cases was a basal cell carcinoma and two others were squamous cell carcinomas. In our series, Case 1 was called a squamous cell carcinoma (low grade) by two pathologists before the patient was referred to the American Oncologic Hospital and its true nature was established. Clinically, the lesion in Case 2 of our series resembled a squamous cell carcinoma, but its true nature was recognized at the time of operation.

We believe that calcifying epithelioma as herein described is benign both clinically and microscopically. However, as can be seen by the case histories above, it can be confused with squamous cell carcinoma of the skin. Malignant degeneration theo-

‡ References 10 and 11.

§ References 19 and 20.

retically could occur, but the possibility of such change is highly remote. The only case in which malignant degeneration occurred in a case of benign calcifying epithelioma has been reported by Gromiko.[14] Calcification and even ossification may occur in a basal cell carcinoma or squamous cell carcinoma of the skin. Such lesions, however, are not to be confused with benign calcifying epithelioma, which is quite a different lesion. This confusion no doubt has existed in the minds of some reporters.

DIAGNOSIS

To establish the diagnosis, the following points are essential: (1) a knowledge of the clinical features and the gross and microscopic features of the lesion; must be obtained; (2) an adequate biopsy of the lesion must be obtained in depth and interpreted by a competent tumor or dermatological pathologist; (3) sebaceous cysts should always be submitted for pathological examination.‖

Only one other lesion resembles benign calcifying epithelioma in its microscopic appearance. That lesion is calcified cyst.

There are those who write in such dogmatic fashion that one is led to believe that the microscopic differentiation between benign calcifying epithelioma and calcified cyst is always simple and clear-cut.

Actually, on the basis of our experience, this is not always the case. In the first place, it is possible that even a large and ostensibly representative piece of tissue taken for microscopic study could lead to confusion (particularly if the lesion is ulcerated) and result in an erroneous diagnosis of a well-differentiated epidermoid carcinoma. Such confusion could not exist with study of the completely excised specimen. The belief that squamous cells cannot be found in benign calcifying epithelioma is not wholly accurate, particularly in ulcerated lesions. However, it can be said that in benign calcifying epithelioma the basal cells are situated internal to or deep to the squamous cells and shadow cells. In epidermal cysts the germinal layer of basal cells is externally placed and the cellular debris is internally situated. It is possible that rupture and trauma of a cyst may distort the usual relationships, but it is unlikely that the direction of maturation will be reversed.

TREATMENT

In most cases of benign calcifying epithelioma the treatment has been simple excision. Recurrence of the lesion is unusual but has been reported. Simple excision of the lesion seems to suffice in most cases.

If the lesion is of some size and involves the scalp and is adequately excised, direct simple closure of the wound will be difficult or impossible. Large scalp lesions are best managed by wide excision, including the skin and underlying tissue down to the pericranium. The defect is repaired by a sliding type of scalp flap.[9] A split-thickness skin graft is applied to the pericranium in the donor site of the flap graft. The scalp flap includes the full thickness of scalp except the pericranium. This type of scalp flap has been successfully used in our institution for many years to cover scalp defects following excision of large areas of the scalp, including the pericranium. Its greatest field of usefulness has been in the management of epidermoid carcinoma of the scalp,¶ where the pericranium, however, is also removed en bloc.

‖ It should be pointed out, too, that rarely a sebaceous cyst may be the seat of an epidermoid carcinoma.

¶ References 3 and 4.

SUMMARY

Benign calcifying epithelioma of the skin is an unusual tumor which was first described and named in 1880. It has been reported at all ages from 3 months to 80 years. The average sex incidence has been about equal. Most of the lesions occur about the head and neck. The growth rate is slow, and the lesion may attain a diameter of from 2.5 cm. to 7.5 cm. in from one to six years. The average duration of the lesion is about 14 months when first seen.

Usually the lesion is a subcutaneous yellowish or grayish firm mass, which may rarely be cystic. In other cases, the lesion involves the skin itself, as seen in Cases 1 and 2 of our series. Microscopically, the lesion is usually encapsulated. The important microscopic diagnostic features are the sheets and groups of mature squamous cells, which may be viable or necrotic; keratinization; foreign body reaction; hyalinization, and calcification. Occasionally bone formation is noted in the older lesions.

We believe that clinically and microscopically the lesion is benign. Grossly, however, on occasion the lesion, especially if ulcerated, may bear a strong resemblance to squamous cell carcinoma of the skin.

Some authors have reported cases of benign calcifying epithelioma which they regarded as squamous or basal carcinomas. We feel that the explanation for this is the fact that calcification and even ossification can and do rarely occur in carcinomas of the skin. These cases should not be included in reports of benign calcifying epithelioma of the skin, but rather should be left in their proper category, carcinoma of the skin.

Only one other lesion resembles benign calcifying epithelioma in its microscopic appearance. That lesion is a calcified cyst. The diagnosis, although usually clear-cut, at times can bewilder the most informed and expert dermatologic or oncologic pathologist. It is understandable then that in some cases the diagnosis arrived at through the evaluation of inadequate evidence could be conjectural.

In the diagnosis of benign calcifying epithelioma, an adequate biopsy is essential. Often the entire lesion must be studied by a competent tumor or dermatological pathologist. In some cases roentgen examination of the involved area may be a presumptive guide in the differential diagnosis. If all lesions clinically thought to be sebaceous cysts were submitted for pathologic examination, more cases of benign calcifying epithelioma would probably be recognized.

When the benign calcifying epithelioma is of the sebaceous cyst type, complete local excision is an adequate method of treatment. When the lesion is ulcerated, wider excision is indicated. When it involves the scalp, as it frequently does, and is of some size, moderately wide excision is advised. Closure is effected by means of a sliding scalp flap.

The world literature has been reviewed. We have been able to collect a total of 117 cases which have been reported by various authors since Ch'in [6] collected and reported 126 cases in 1933. This brings the total number of cases of benign calcifying epithelioma reported in the world literature from 1880 to 1950 to 243 cases. Three new cases are herein reported and added to the American literature.

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SCALP THICKNESS AND THE FAT-LOSS THEORY OF BALDING

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OF THE various hypotheses advanced to account for male pattern balding, most have been rendered untenable by the simple demonstration that testicular hormones are a prerequisite for the common patterned alopecia of the male. As shown by Hamilton, castrate or eunuchoid males are free from pattern balding, while testosterone can induce hair fall in genetically susceptible castrates or eunuchoids. Moreover, hair fall can be checked by castration, so that postpubertal castrates exhibit less hairline recession than normal controls of comparable age.* Therefore, tight headgear, exposure to the elements, and lack of hair care no longer need be blamed for the patterned loss of hair in the male, and ketonic steroids rather than obscure micro-organisms seem to be the mediating factor. What is not clear is just how masculinizing sex hormones act upon the follicles or the supporting tissues to bring about patterned loss of hair.

In an attempt to explain how sex hormones play a role in male balding, interest has been revived in the possible relationship between scalp looseness and thickness, and luxuriance of the hair. Kohl-Pincus and Schein both reported a sex difference in the thickness and looseness of the scalp, and suggested that the amount of hair is inversely proportional to the scalp tension, and varies directly with scalp thickness. M. Wharton Young, seeking an anatomical explanation for balding, also invoked scalp tensions and tissue thicknesses, and reported (by way of evidence) "a direct relationship between the thickness of the scalp and the amount of hair it contains." Szasz and Robertson further elaborated along this line. According to them, the scalp is thicker and fatter in the female, while the hormonally mediated loss of subcutaneous scalp fat in the male makes him more susceptible to vascular changes arising from long-continued scalp tensions, and therefore more prone to balding. Thus, their theory seemingly accounts for the male-limited nature of pattern balding.

Now it is true that the subcutaneous fat layer is generally thicker in the female, during childhood and in adult life as well. There is, moreover, experimental evidence that anabolic sex hormones can reduce the thickness of the subcutaneous fat.

From the Fels Research Institute.

* Garn, S. M., and Gertler, M. M.: Unpublished data

But it is not known whether scalp thicknesses parallel subcutaneous fat thicknesses elsewhere on the body, nor is it known whether the scalp is thicker in the female than in the male. Evidence for a circumpubertal decrease in the thickness of the male scalp has not been forthcoming. And no quantitative comparison of scalp thicknesses in bald and luxuriantly haired men has yet be published. Obviously, the validity of the "fat-loss theory" of balding rests on plausible but yet unverified assumptions.

It is the purpose of this paper, then, to present data on scalp thickness as measured on teleoroentgenograms of boys and girls, men and women, and on a matched-pair series of bald and nonbald men, in order to settle the points in question.

MATERIALS AND METHODS

The present study is based on over 1,700 serial head x-rays of 523 healthy subjects from 4 years to 69 years of age. The 236 children and subadults measured were, with few exceptions, either participants in the Fels longitudinal studies, or siblings of participants. The 135 adult women

TABLE 1.—*Tabulation of Subjects by Age and Sex*

Age Group, Yr.	Males *		Females	
	No. Persons	No. Observations †	No. Persons	No. Observations †
4–7	86	213	101	265
8–11	84	205	85	231
12–15	82	134	62	163
16–19	38	88	41	95
20–29	18	22	37	43
30–39	11	12	52	58
40–49	34	37	37	39
50–59	15	16	8	8
60–69	3	3	1	1

* Not including the matched pairs.
† Based on serial lateral-skull x-rays of children aged 4 to 19 years and 269 x-rays of 246 adults.

were all mothers of participants in the Fels studies, while the 152 adult men included both fathers of Fels participants and 37 others, primarily faculty or students at Antioch College, or members of the Fels Institute Staff. All subjects were white, American born, and the majority were natives of southwestern Ohio. Individuals with congenital ectodermal defects, or nonpatterned alopecias were excluded from the study. A complete tabulation of subjects by age and sex is given in Table 1.

Measurements of scalp thickness were made on lateral skull x-rays taken at a standardized tube-to-film distance of 60 in. (152 cm.) (except as noted below). Exposures varied from 18 to 32 ma.-sec. and 47 to 60 peak kv., according to age and head breadth. A vernier caliper (Fisher No. 12-130) with the measuring tip ground to a point, as described by Garn and Saalberg, was used throughout. A supplementary light, similar to a dense-film visualizer, mounted within the x-ray illuminator, aided in the measurement of the darker x-rays.

Scalp thickness measurements were made at the level of the frontoparietal junction (bregma), a true landmark ordinarily visible upon lateral skull x-rays. This point was chosen partly because it is a true anatomical point, and partly because the scalp at bregma does not include muscle layers as is true in the frontal and occipital regions. The measurements, taken at right angles to the skin surface as shown in Figure 1, were made either at bregma, or slightly anterior to this landmark to avoid the V-shaped suture depression, noticeable in about 20% of the lateral skull plates.

In order to compare scalp thicknesses in bald and nonbald men, a special matched-pair series was set up. This series included 21 men between 18 and 44 years of age, all of whom exhibited early male-pattern balding, and 21 men with luxuriant hair, individually matched with members of the bald group on the basis of age. The pairs were matched to the nearest year; the two groups (bald and nonbald) therefore averaged about the same in mean age (32.4 and 32.0 years, respectively). The degree of hair recession was determined quantitatively, as the distance from nasion to hairline, as measured on the x-rays, using a Keuffel and Esser No. 55 map reader. A small lead dot, affixed to the most posterior point of hair recession prior to each x-ray, assisted in locating this hairline point in the skull plate. The mean nasion-hairline distance was 10.5 cm.

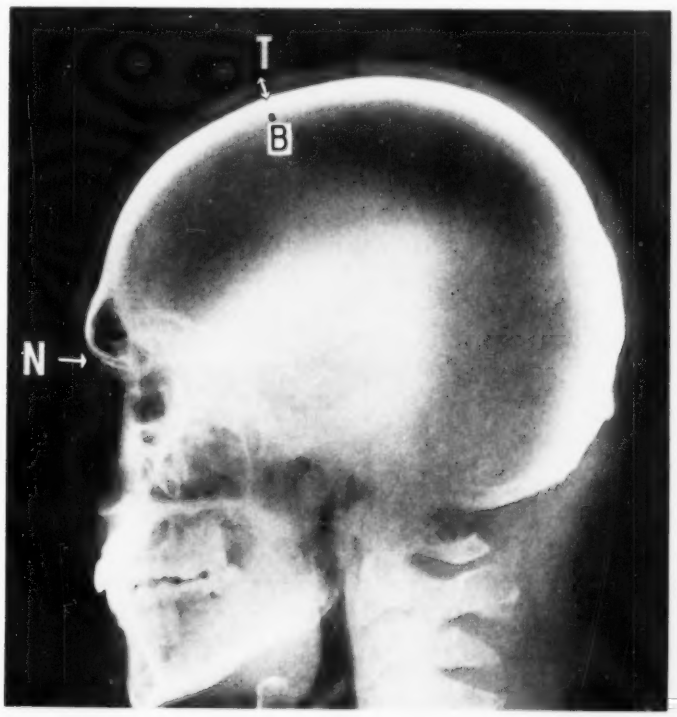

Fig. 1.—Lateral skull x-ray showing scalp tissue and points mentioned in the text. *N*, nasion; *B*, bregma. Scalp tissue thickness at bregma (*T*) is indicated by an arrow.

for the nonbald group and 20.5 cm. for the bald group, thus documenting the greater hairline recession of the latter.

Two technical points should be mentioned here, the systematic error of measurement due to magnification, and the reliability of the measurements themselves. In the x-rays taken at 60 in., the error due to magnification is approximately 5%, and, being constant throughout, was not corrected for. The matched pair series, taken at 72 in. (183 cm.), has a slightly smaller magnification error (4.4%) and is therefore considered separately. For practical purposes, however, the two groups are comparable.

Reliability of measurement was investigated by comparing scalp thickness measurements on 31 adults who had been x-rayed on two separate occasions, averaging nearly four years apart. The correlation between the paired measurements for these 31 adults was 0.98, indicating a high degree of reliability for the measurements of scalp thickness as made in this study.

FINDINGS

The measurements of scalp thickness at bregma were first sorted according to age and sex, in order to determine the extent and direction of changes from childhood through advancing age.

When this was done, it was observed that the average scalp thickness increased, in both sexes, between the fourth year and the fourth decade. Thereafter, there was evidence for a slight decrease (Table 2). The actual amount of increase was considerable, averaging 2.7 mm. in the males and 2.3 mm. in the females, or 73% and 61% above the initial values. As shown graphically in Figure 2, the increase was most rapid during the earlier years (amounting to 0.2 mm. per year), and was much slower during adulthood (amounting to 0.4 mm. per decade postpubertally). The trend for both sexes was therefore towards increasing scalp thickness from childhood until middle age.

Comparing males with females, the average scalp thicknesses were equal during the first decade; thereafter the males had thicker scalps. From 4 to 11 years, the

TABLE 2.—*Scalp Thickness in Millimeters at Bregma by Age and Sex*

Age Group, Yr.	Males			Females		
	No.	Mean	Standard Deviation	No.	Mean	Standard Deviation
4-7	213	3.7 ± 0.04*	0.55	265	3.6 ± 0.04	0.62
8-11	205	4.3 ± 0.04	0.71	231	4.3 ± 0.05	0.69
12-15	134	5.4 ± 0.06	0.84	160	5.1 ± 0.05	0.79
16-19	88	5.9 ± 0.08	0.75	95	5.5 ± 0.09	0.76
20-39	64	6.4 ± 0.14	1.11	101	5.8 ± 0.12	1.17
40-69	56	5.8 ± 0.16	1.25	48	5.6 ± 0.15	1.05

* Standard error $\frac{\text{S. D.}}{\sqrt{\text{N-1}}}$.

differences were not significant. In the next age group (12 to 15) male scalps averaged 0.3 mm. thicker. This difference increased to 0.4 mm. at 16 to 19, and reached a maximum of 0.6 mm. in the third and fourth decades. These sex differences are statistically significant at better than the 1% level of confidence and indicate that male scalps tend to be thicker than the scalps of females. And even in the fifth and sixth decades, the males continued to exhibit greater scalp thicknesses.

The possibility of a male-limited circumpubertal loss of scalp substance was further investigated by the longitudinal method. To do this, data on 20 boys and 20 girls for whom serial x-rays were available from the 11th to the 16th year, were recomputed as a percentage of the 11-year values. However, as shown in Figure 3, both boys and girls exhibited a consistent increase in scalp thickness, reaching 130% of the 11-year values. Thus the longitudinal method confirmed the cross-sectional studies and showed that scalp thickness increases during puberty in boys and girls alike.

Finally, the relationship between male pattern balding and scalp thickness was investigated directly, with use of the technique of matched pairs. Twenty-one men, between the ages of 18 and 44, all of whom exhibited unmistakable evidence of early male pattern balding, were individually matched for age, with 21 men with luxuriant

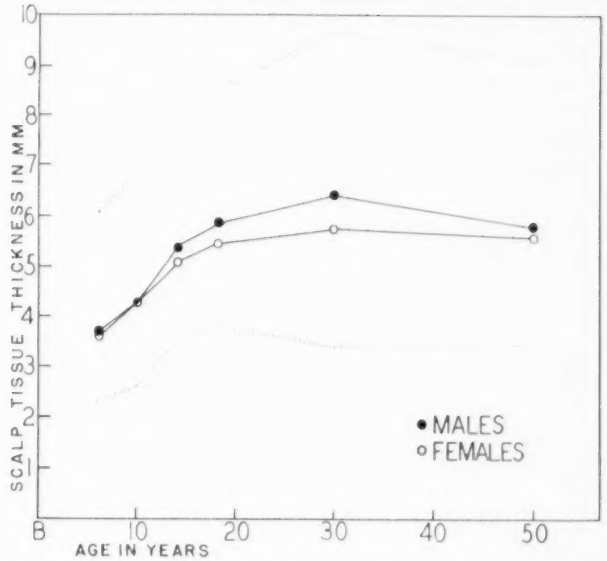

Fig. 2.—Age and sex differences in scalp thickness. Means for males are indicated by solid symbols, females by open symbols. The dotted lines indicate the extreme values (range) for each age group.

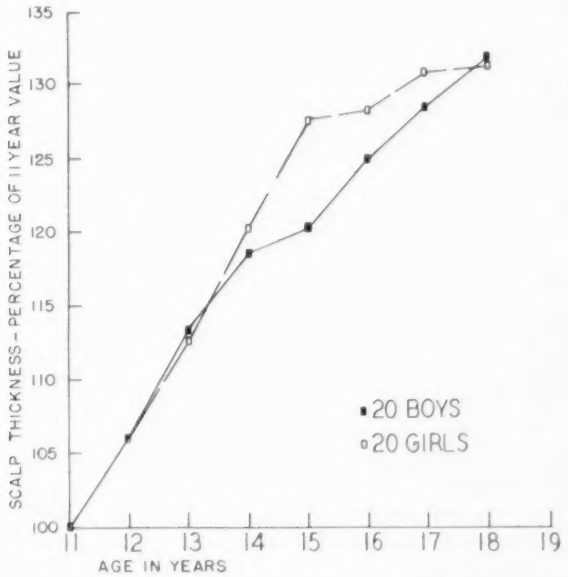

Fig. 3.—Percentage change in scalp thickness of 20 boys and 20 girls from the 11th through the 18th year.

hair (Table 3). The bald men averaged considerably higher in hairline recession (21.5 cm.) than the nonbald men (10.6 cm.). In age, the mean difference (0.4 years) was negligible. And in scalp tissue thickness also, the difference (0.1 mm.) was both negligible and not statistically significant, being but one-third as great as the standard error of the difference. Thus there was no evidence that bald men have thinner scalps than men of comparable age but with luxuriant hair.

It was observed that scalp tissue at bregma is generally thicker than scalp tissue at the midfrontal region. However, since this was true in childhood, in adult men and women, and in the bald men as well, this thickness gradient does not seem to be related to pattern balding.

TABLE 3.—*Scalp Thickness in Millimeters at Bregma in Bald and Nonbald Men Matched on the Basis of Age*

	Bald Series		Nonbald Series		
Pair No.	Age, Yr.	Scalp Thickness	Age, Yr.	Scalp Thickness	Difference 2-1
1	18	5.9	19	5.9	0.0
2	19	7.4	20	4.3	−3.1
3	22	6.6	22	7.1	0.5
4	24	4.4	24	5.3	0.9
5	26	5.6	26	4.3	−1.3
6	28	4.5	28	7.5	3.0
7	31	5.6	30	4.3	−1.3
8	32	5.9	31	5.7	−0.2
9	32	4.8	31	5.3	0.5
10	32	6.9	32	4.2	−2.7
11	33	6.0	32	6.2	0.2
12	34	4.7	32	6.5	1.8
13	35	5.5	34	6.6	1.1
14	35	5.5	34	4.8	−0.7
15	35	6.5	35	4.6	−1.9
16	36	4.4	36	6.1	1.7
17	38	4.7	39	5.5	0.8
18	41	4.7	40	6.0	1.3
19	42	5.4	41	7.1	1.7
20	43	5.5	42	4.8	−0.7
21	44	5.9	44	5.8	−0.1
Mean ± S. E.	32.4 ± 1.6	5.5 ± 0.2	32.0 ± 1.5	5.6 ± 0.2	0.1 ± 0.3

The findings, then, failed to confirm the notions that the male scalp is thinner, that there is a circumpubertal loss of scalp substance in the male, or that bald men have thinner scalps. In fact, the males tended to have thicker scalps; scalp thickness increases in both sexes during puberty, and scalp thickness does not vary with the extent of patterned hair loss.

COMMENT

The findings reported here leave little doubt that the thickness of the scalp increases from childhood through the adult stage, and there is no evidence in the data for a pubertal or postpubertal loss of scalp tissue in the male. In fact, males seem to have thicker scalps throughout life. And when bald men and men of comparable age but with luxuriant hair are compared, no significant difference in scalp thickness can be discerned. It seems safe to make the generalizations that men and not women have the "fatter" scalps (thus contradicting Rattner's summary), and that scalp thickness and the extent of pattern balding are unrelated.

These findings are surprising, in that they constitute one apparent reversal of trend. Females generally have thicker subcutaneous fat deposits. After childhood, the subcutaneous fat thickness of the female is approximately twice that of the male, excluding the mammary and trochanteric fat pads. Therefore, the greater thickness of the male scalp observed here may represent a secondary sexual characteristic akin to the cephalic fat deposits in the male gorilla. While it is possible that the differential may be due to a tissue constituent other than fat, the general relationship between scalp thickness and subcutaneous fat (in our material) tends to support the belief that much of the variance is attributable to fat.

These findings are completely at odds with the brief reports of M. Wharton Young (except for a tendancy for the scalp of the forehead to be thinner than the scalp tissue elsewhere). Since M. Wharton Young has published neither his data, nor his investigative techniques, it is not possible to explain the divergence in findings. However, our findings on the scalp thickness at bregma correspond closely to the data of Todd and Kuenzel, even though their investigations were based on the cadaver and they did not use the roentgenographic technique. And the sex difference in scalp thickness, observed here, is in accord with the earlier findings of Gladstone as reviewed by Stewart. It is therefore difficult to reconcile Young's reports with our findings, and the others mentioned.

Since the Szasz-Robertson "theory" involves habitual muscular tensions arising out of environmental stresses, our findings do not bear upon their paper in its entirety. However, to the extent that they assume a hormone-medicated, gene-limited tendency for males to lose scalp substance, and relate fat loss to the mechanism of balding, these steps in their general theory may be challenged.

It should be observed, however, that the microanatomy of the scalp cannot be investigated by the roentgenographic technique, at least on the living. Changes in vascular tone, infiltration of subcutaneous tissue by connective tissue, and other histological alterations discussed by Light cannot be excluded. Nevertheless, we have been able to settle the points in question: Males have thicker, not thinner, scalps. Males do not lose scalp substance at puberty. And scalp thickness and male pattern balding are not related variables.

SUMMARY AND CONCLUSION

Scalp tissue thickness at bregma was investigated through the use of soft-tissue x-rays on 523 subjects aged 4 to 69 years, including 21 pairs of men matched for age, but differentiated by the amount of hair loss. It was found that males either equalled females in scalp thickness, or (after the first decade) exceeded them. There was a constant increase in scalp thickness, in both sexes, through the fourth decade. No evidence for a sex-limited pubertal or postpubertal decrease in scalp tissue was found. Though differing markedly in the degree of hairline recession (bald men 21.5 cm., nonbald men 10.5 cm.), the pairs did not differ significantly in scalp thickness. It was concluded that the fat-loss theory of male pattern balding cannot be substantiated and that more elaborate theories involving this assumption therefore cannot be accepted.

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ACUTE AND CHRONIC REACTIONS TO BLACK FLY BITES (SIMULIUM FLY)

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A GROUP of similar but unfamiliar eruptions were noted among soldiers and their dependents in Tokyo. Japanese personnel identified some of the lesions as "buyo bites," and these were subsequently identified as inflicted by a species of Simulium or black flies.

Stokes [1] (1914) wrote a complete article with a comprehensive bibliography on the early reactions to these insects. Winkler [2] recently observed severe erythematous and edematous reactions persisting for one week in patients in Germany. Our patients also showed these typical early reactions, but many eruptions persisted from 3 to 16 months and demonstrated several types of dermatoses.

Of 600 known species of black flies, 15 are found in Japan.[3] One of the commonest species is the same Simulium venustum Say reported by Stokes.[1] Sasa [3] states the other common types are Simulium japonicum Matsumura and Simulium nipponese (Shiraki). Stone * states that the specimens collected around Tokyo were identified by him as follows: (common) Simulium venustum Say, Simulium saliopiense Edwards, and Simulium spp; (uncommon) Simulium iwatenis Shiraki, Simulium latipes Meigen, Simulium tuberosum Lundstroem, Simulium bidentatum Shiraki, and Simulium nipponese Shiraki. However, he emphasizes that definite biting records must be kept to establish the pests. While this is important, it was not done in our cases. Simulium venustum Say has been previously established as a pest. The Simulium flies are blood-sucking insects, but the females (only) are vicious biters. Although Onchocerca volvulus Leukhart is carried in some species in Africa, no known disease of man is carried in Japan. Black flies are tiny insects (1 to 5 mm. long) [3] with six blade-like piercing mouth parts in the female; the small body is hump-like [4]; the antenae have 10 to 11 joints; a characteristic wing venation is useful in classification, and thick short legs are present. They breed in flowing streams or ditches, where they cling to debris. In the summer, the eggs hatch in five days; then larvae emerge and require 3 to 10 weeks for development before the brief pupal period of 3 to 6 days. When optimal conditions are met, the pupa forces its way out of its pupal case and, surrounded by a bubble of gas, rises to the surface of the water and flies immediately. Five to six generations may be produced each season.

From the Dermatology Section of Murphy Army Hospital, Waltham, Mass. (Major Gudgel), and Letterman Army Hospital, San Francisco (Colonel Grauer).

* Stone, A.: Personal communication to the authors, June 18, 1953.

The range of the insect is rather small, usually 1,000 yards, but with a strong wind it may go one mile from its breeding place. Grassy golf courses and shady wooded areas are commonly populated by flies, but many of the bites occurred in a dependents' housing area in the suburbs of Tokyo. Most of the bites were inflicted around sunrise or sunset. The bites occurred most commonly after rain. Fortunately, the insect does not usually enter a house.

Stokes [1] had noted the impression that "the bite of the fly loses its virulence as the season advances." He speculated on the immunity in the host or change in the fly's virulence. Jamnback,[2] however, has demonstrated in New York state that of 17 species present there, only 3 were annoying to man, and these were present in large numbers only during part of the season. By treating streams twice (late April and early June) with a chlorophenothane (D.D.T.) fog from an airplane to kill the larval stage, these annoying species are removed. Thus it is important that the species be exactly known.

The bites seen in Japan were present mainly on the legs and arms (exposed areas). Among Japanese wearing wooden sandals, the back of the heel was bitten. Multiple bites are made possible because of the tiny size of the insect, its persistence, and the painlessness of the puncture. The fly will feed from 40 to 60 seconds if not disturbed. It is believed that the fly injects an anesthetic anticoagulant. For so small a fly, the hemorrhage is severe, and often the first warning is a trickle of blood. The normal course of the reaction is a small ecchymosis with a blood crust, followed in several hours with a small pruritic papule that persists several days and disappears without any residual lesion. Other persons develop erythema and large wheals that slowly enlarge to 1 cm. Occasionally, the tenderness and appearance resemble a bruise. Less commonly, a severe acute reaction is seen.

REPORT OF CASES

CASE 1.—Our Japanese secretary had two typical attacks last summer. The bites on the feet, posterior ankles, and lower legs were not noted for several hours. Then she noted small wheals with a hemorrhagic center. These rapidly enlarged until the lower legs were twice their normal size; they became erythematous and so acutely tender, that walking was difficult. She had a fever of 101 F. and developed enlarged, tender femoral lymph nodes. The swelling, fever, and adenopathy disappeared after several days. Some of the bites remained visible as small papules for 7 to 10 days.

Some subacute cases have been noted with pruritic papules and wheals with central vesicles at the punctum. Pruritis is especially intense and excoriations keep lesions raw and retard healing. Satellite vesicles form around the central lesions forming large weeping patches with crusting. Healing occurs in 2 to 8 weeks with flat shiny cicatrix formed.

CASE 2.—A 27-year-old white woman was bitten by black flies on the arm with initial normal reaction to bite. However, lesions failed to heal completely, and after five weeks, induration of bites was noted, accompanied by severe pruritus and deep-seated vesicles. Biopsy of a lesion was performed one week later.

Histopathology.—Epidermis: There is hyperkeratosis, parakeratosis, plus a serous crust. Intercellular edema is present with small vesicles filled mainly with lymphocytes and an occasional eosinophile. The rete pegs and papillae are elongated.

Cutis: There is a moderate chronic inflammatory infiltrate composed mainly of lymphocytes plus a few plasma cells and eosinophiles. Infiltrate is perivascular and periglandular and extends to the upper subcutaneous fat.

Fig. 1 (Case 2).—Six weeks' reaction. Vesicular formation in epidermis with chronic inflammatory changes throughout the epidermis; × 125.

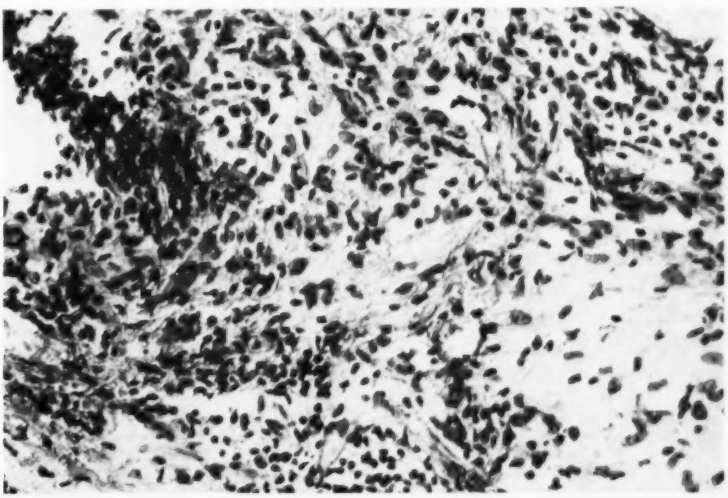

Fig. 2 (Case 2).—Demonstrates the dense chronic inflammatory changes (lymphocytes and histiocytes with occasional eosinophile); × 408.

Treatment.—Treatment consisted of 3% iodochlorhydroxyquin (Vioform) cream and lotion. Lesions involuted very slowly over a six-month period. During this time, patient also developed a contact dermatitis due to the dye in denatured alcohol used in the obstetric clinic. The latter responded quickly to bland therapy.

Persistent lesions have been observed in nine patients. The duration of the lesions was 6 to 11 months. Two distinct reaction patterns have been observed, with some cases having features of both.

The commonest type has been corymbiform nodular vesicular patches with associated lesions indistinguishable from nummular eczema. The anterior lower legs have been most commonly involved, although the arms and, in one case, the neck have been affected. The latter case was not originally recognized as due to black fly bites.

Case 3.—An 8-year-old white boy with history of personal and familial atopy was treated for an infectious eczematoid dermatitis of the neck and arms for several months before a similar eczematoid patch developed around a recognizable "buyo bite" on the leg. The boy then stated that the other lesions followed bites, too. Any bite on the body produced a flare of the chronic lesions. Strict preventive measures were taken to avoid further bites, and the lesions healed over a period of weeks.

Hard, pigmented, rough, pruritic nodules characterized the other type. Unless scratched and secondarily infected, these remained relatively quiescent. The periphery of the lesions had a few vesicles and crusts, but frank eczematization rarely occurred. The Japanese have named this type "urticaria perstans verrucosa." Healing ultimately occurs with scarring and pigmentation.

Case 4.—A 22-year-old Nisei woman was seen with firm, crusted nodules on both lower legs. Lesions had been present with little change for seven months. She had noted blood-crusted lesions in early September, 1951, while playing golf. There was little change under previous therapy of calamine lotion and an antihistamine ointment. Occasionally, small vesicles and eczematization were noted, but the main lesions remained pruritic nodules.

Histopathology.—Epidermis: There is hyperkeratosis, parakeratosis, and a serous exudate containing mononuclear cells. Intercellular edema is present with intraepidermal vesicles containing eosinophiles, polymorphonuclear leucocytes and mononuclear cells, mainly lymphocytes. Acanthosis is present, with elongation of both the rete pegs and papillae. Pseudoepitheliomatous hyperplasia was noted in several areas.

Dermis: Perivascular infiltrate, mainly mononuclear cells—lymphocytes and histiocytes, plus some eosinophiles—and polymorphonuclear leucocytes, is present, particularly in the upper corium.

Treatment.—The lesions involuted and pruritus ceased after x-ray (75 r weekly for a total of 450 r) and local bland therapy were given. In a similar case, 225 r x-ray caused early disappearance of chronic lesions.

Therapy of all stages of this disease is essentially palliative. Oral antihistamines, compresses (hot or cold), shake lotions, and elevation of the involved part are used during the acute stage; 3% iodochlorhydroxyquin with 40% pine tar in Lassar's paste is beneficial during the chronic phase, and x-rays are very effective in hastening the involution of indurated plaques and in relieving the itching.

However, all chronic lesions may show exacerbations with nummular-type eczematization as long as any trace of the "mother lesions" remains.

Rockwell and Johnson [6] observed immediate wheals, late papular reactions, and vesicles, bullae, extensive edema, and erythema resembling cellulitis associated with lymphadenitis in mosquito bite reactions. Corticotropin and, to a lesser degree,

cortisone decreased the severity and chronicity of these allergic reactions. We have had no experience with these drugs in black fly dermatitis.

Desensitization was not attempted in our patients. Stokes [1] found that sensitive patients reacted to a glycerin emulsion of the head parts with a 1-cm. papule and a 1 to 2 in. (2.5 to 5-cm.) erythema. The toxic product was not soluble in alcohol, not destroyed by drying or heating, or by 0.5% sodium bicarbonate, but it was destroyed by 0.25% hydrochloric acid and pancreatin. Patton and Evans [7] (1929) suggested that a toxic enzyme was present in the saliva.

However, the allergic nature of arthropod bites has been recognized in many species. Rockwell and Johnson,[6] while finding some irritation in mosquito bites, also found three types of allergic reaction: urticarial, tuberculin, and eczematous. These frequently occurred in persons with an allergic background. Many of the patients with chronic reactions seen by us also had an atopic history. Multiple allergens were felt to be present in the mosquito reactions rather than a single type.

Hocking [7] quotes de Meilla, Heilesen, and Gordon and Crewe as having found an allergic nature to these reactions. He further states that Georgevitch produced a toxin protecting animals. The preparation of antigens suitable for experimentation involves special considerations. Briefly, these include (1) use of a species known to be a pest and one that produces reactions in susceptible people; (2) question of use of wild or laboratory species—i. e., wild species may have fed on man and theoretically laboratory species might not reproduce the expected dermatoses; (3) exclusive use of female flies.

After an antigen is selected and prepared, there must be a careful choice of subjects for controls and study.

Factors which appear important in the individual differences to the black fly include (1) attractiveness of the individual to the fly; (2) species of Simulium; (3) allergic background of the patient.

Naturally, a great amount of interest has been shown in the great variations seen in apparent freedom from attack that some people enjoy. Winkler [2] noted that three people were camping and surrounded by black flies, but only one person was attacked. The nonattacked were smokers. The only known physiological factors in attraction of flies are increase of carbon dioxide and colors. Delmat [5] undertook artificial culture of black flies, controlling temperature and humidity and using sheer black cloth to produce a mottled shade. Wild and laboratory-raised flies were used but, although some biting was observed, none oviposited. Then the flies were exposed to carbon dioxide gas. Following this, the females attacked human subjects voraciously, mated and many oviposited four to six hours after exposure to the gas.

Stokes [1] and Sasa [3] have both noted heavily infected country people develop immunity to the bites. This observation has not been scientifically checked, as the apparent immunity may be due to changing seasonal species as noted by Jamnback.[8]

Chadwick † summarizes the attraction factors of insects as follows:

"Carbon dioxide . . . [is] a factor in attracting some mosquitoes under certain conditions in the field.

"Color . . . [There is] some suggestion that dark objects are more attractive than light ones.

"Moisture . . . This is all mixed up with the question of sweating rates for different individuals and on different parts of the body. . . . The possibility [exists] that other con-

† Chadwick, L. E., Personal communication to the authors, June 26, 1953.

stituents of sweat may act as attractants or repellents, etc. Wounds and blood are known to play a part in attraction [for] cattle.

"Movement . . . moving objects [may] be more attractive.

"Skin temperature, individual host differences, weather factors (light intensity, wind velocity, temperature and relative humidity, barometric pressure and time of day) and physiological state of the insect are other factors in effecting biting."

Prevention is possible by using repellents like dimethylphthalate or newer chemical types now available. However, the repellent must cover all exposed areas, as the insects will bite untreated areas even if the repellent surounds the spot. Sweating dilutes the repellents and makes them less effective. D. D. T. solution has been used used to destroy the fly and also its larvae in breeding areas.

Hocking [9] feels that the psychological effects of biting fly attacks may be serious. In black flies, this is due to the continual noise and impact of the flies, the manual removal reaction to this, and the known effects of the bites. Group efficiency and morale is rapidly lowered. Panic may lead to running away from the flies (which, however, is occasionally effective by running into the wind). Although there are many references,‡ to heavy swarms killing animals, no such events were observed locally. Indeed, no large swarms were observed. This may be due to the many easily accessible victims in the Tokyo area and thereby the dispersal of the flies which might otherwise gather in swarms to attack other individuals.

The histopathology noted in our cases completes the picture of reaction to the black fly. Stokes [1] performed biopsies on 4- and 24-hour and 5- and 18-day-old lesions. He found that the principal changes were in the corium, consisting of vascular dilation, edema, and polymorphonuclear leucocytic perivascular infiltrate with a high eosinophilia early, but with an increase in mast and small round cells in the older lesions. The epidermis showed edema and "pseudovesicles" plus occasional true vesicles. This is similar to the pathology of the mosquito bite observed by Rockwell and Johnson [6] except that a lymphocytic infiltrate was noted earlier by them.

Our biopsies at six weeks and seven months showed marked epidermal changes including hyperkeratosis, parakeratosis, serous crust, intracellular edema with true vesicle formation, elongation of rete pegs and papillae, plus a chronic round cell infiltrate containing eosinophiles with a predominating distribution around blood vessels and glands and extending throughout the corium.

This is similar to the insect bite reactions noted by Lever,[10] but there was no tendency for lymphoid follicle formation nor were there mitotic histiocytes or epidermoid inclusion cysts in our cases.

SUMMARY

Many insect bite reactions due to Simuliid flies were noted around Tokyo. These consisted of immediate pruritic blood-crusted nodules, giant urticarial lesions associated with constitutional symptoms, eczematoid lesions, and chronic lesions that were corymbiform nodular-vesicular plaques or hard verrucoid nodules.

The allergic and immune reactions are discussed with mention that species must be accurately determined to check differences in fly bites. All species do not produce reactions.

‡ References 1, 2, and 9.

The late histopathologic changes show that acute changes persist in the epidermis although a chronic inflammatory reaction replaces the earlier acute polymorphonuclear reaction in the corium.

Methods for treatment, control, and future investigations are discussed. Ultimate protection from black fly bites should develop from the consideration of the physiology and species identification of the fly and the allergic-immunologic studies of the patient.

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BARBER'S INTERDIGITAL PILONIDAL SINUS

The Incidence, Pathology, and Pathogenesis

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A BARBER with a "subepithelial inclusion cyst" in the interdigital web, caused by hairs acting as foreign bodies, was twice presented to the San Francisco Dermatology Society in 1942.* Since then 6 additional reports of this condition have been published, making a total of 10 cases in the literature. Our attention was directed toward this occupational disease by a patient with multiple lesions and complications to be described below.

INCIDENCE

Our complicated case was presented at the 1952 meeting of the Pacific Dermatological Association, at which there were approximately 150 dermatologists. Only two such cases were recalled by the group, one of which had been reported. For this reason, it was believed that the condition was rather uncommon; however, Waisman and Olivetti [3] state, "presumably the condition is more prevalent than the few reported cases would indicate, because to many of the victims such a relatively trivial and non-disabling occupational event hardly merits seeking medical consultation." Patey and Scarff † reported a case and made the following statement:

> Our patient said that a friend of his, also a barber, had a similar condition, which arose in the same way, so we sought for further examples. Assistants in two well-known London hairdressing firms said that it was not at all uncommon for minor infected lesions to be produced owing to the puncture of the skin during hair cutting, particularly in the hand. Usually they clear without serious trouble after the removal of the hair. Occasionally, however, a more chronic lesion resulted, and we were told of one such case in which legal action followed; but we could not trace the legal record. From our inquiries it is obvious that among barbers hair is well recognized as a traumatic and infective agent.

Downing,[6] on the other hand, in the report of a case from Boston stated, "I think it must be rare in this country."

Because of the disagreement on the incidence, arrangements were made with the Barbers' and Beauticians' Union, and 115 barbers in the San Francisco area were examined. They were visited in their shops under actual working conditions. Fifteen

From the Division of Dermatology, Department of Medicine (Dr. Joseph) and the Department of Pathology, (Dr. Gifford) Stanford University School of Medicine, San Francisco.

* References 1 and 2.

† References 4 and 5.

barbers were found who had interdigital pilonidal sinuses (not including our case described below). One had three and three others two each, making a total of 20 lesions in the 15 barbers (Table 1).

CLINICAL APPEARANCE AND COURSE

In the 15 affected barbers, the clinical appearance of the lesion was that of a small, symptomless opening on the dorsum of the interdigital web. It was often tiny, barely visible to the unaided eye, and appeared as a small black dot due to the short hairs which either protruded or could be expressed. No opening over 1 mm. in diameter was found. Eight of the barbers did not know the lesions were present until found by the examiners. In these cases there was no inflammation, tenderness, or redness. Inflammation was found in only two cases (F and N).

TABLE 1.—*Incidence Among Barbers*

Case	Lesions, No.	Site	Duration	Years as Barber	Barbers in Shop
A	1	L_3	2 yr.	20	2
B	2	L_2 L_1	1 yr. ?	8	3
C	1	L_2	?	33	4
D	1	R_1	?	35	1
E	1	R_4	?	14	1
F*	1	L_4	?	3	3
G*	1	R_2	"Several years"	40	3
H	3	R_1 L_4 L_1	? ? 2 weeks	50	1
I	1	L_1	?	41	5
J	1	L_3	?	50	2
K	2	L_2 R_3	1 year 1 year	7	2
L	1	L_1	?	51	2
M	1	R_3	?	10	2
N	1	L_3	?	22	1
O	2	L_1 R_2	2-3 months	2½	2

* Cases F and G in same shop.

When the affected web was picked up between the examiner's fingers, a small cyst-like nodule could be palpated in the skin under the opening in eight cases. These were estimated to be 3 mm. or less in diameter except in one (H), in whom the nodules were from 5 to 8 mm. in diameter. The expressed hairs were generally from 1 to 3 mm. in length and often of different colors (Fig. 7). In several cases, there was slight scaliness with a "collarette" of scales around the opening. Where the underlying nodule was larger, there was a small hillock or "pouting sinus" (Fig. 1). Four had multiple lesions.

The complicated case which directed our attention to this condition was that of a patient who experienced considerable difficulty due to the development of six sinuses over a period of five years. This barber, 36 years of age, had been engaged in his profession for 20 years. The initial lesion in the right second interdigital web had been destroyed by electrodesiccation, leaving a scar. The second, in the left second interspace, became infected, while the third, in the left fourth interspace, remained small and uncomplicated. The infected lesion was incised and large numbers of

small hairs removed, and a palmar abscess developed requiring treatment with penicillin given intramuscularly. Subsequently both lesions on the left hand were excised widely. Ten months later, there were redness and tenderness in the old electrodesiccation scar in the right second web, and short hairs protruded from a pinpoint opening. There were four similar openings with protruding hairs in the surgical scar in the left second web (Fig. 2). Thus, the fourth and fifth lesions were recurrent and developed in scars. Finally, a new "pouting sinus," noninflammatory and hair-bearing, formed in the left third interspace (Fig. 1). Considerable time was lost from work, and when last seen the patient was considering changing his occupation.

As shown in our case and those reported by others, interdigital pilonidal sinuses do not always remain "trivial and nondisabling." Infection, with abscess or cellulitis, occurred in ours and in at least 5 of the 10 cases culled from the literature. (Recur-

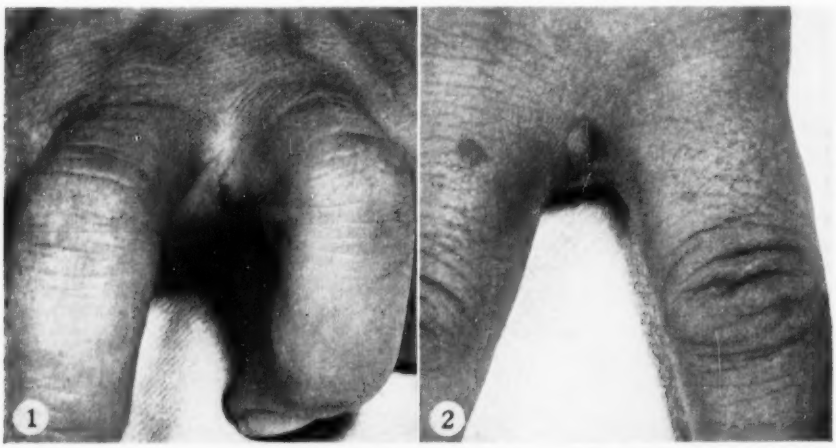

Fig. 1.—"Pouting sinus" type lesion with cystlike nodule.
Fig. 2.—Four small hair-bearing openings in scar (photograph reversed in processing).

rence of hair-bearing sinuses in surgical scars, as reported here, appears to be unique.) There was no question of compensation, since our patient was self-employed, but Patey and Scarff reported a compensation problem [4] and it is readily seen how this could arise.

The course of the condition in those with noninflamed lesions is apparently one of the utmost benignity, although one barber had a noninflamed lesion which had remained for at least two years. It is surmised that many heal spontaneously once the hairs are removed. That the course may be one of recurrences, repeated secondary infection, and chronicity despite treatment has been shown.

PATHOLOGY

There is considerable variation in the structure of the lesions of interdigital pilonidal sinus, but all the different changes would seem to be related and probably sequential. The simplest, commonest, and presumably earliest change is the imbed-

ding of a hair in the epidermis, with a thickening of the epidermis around it (Fig. 3). A portion of the hair may penetrate through the epidermis and into the underlying dermis (Figs. 4 and 5). Hair lying free in the dermis, regardless of the manner in which it came to lie there, will incite a foreign body reaction. The next change follows the one just described. It consists of the forming of a pit-like depression of the

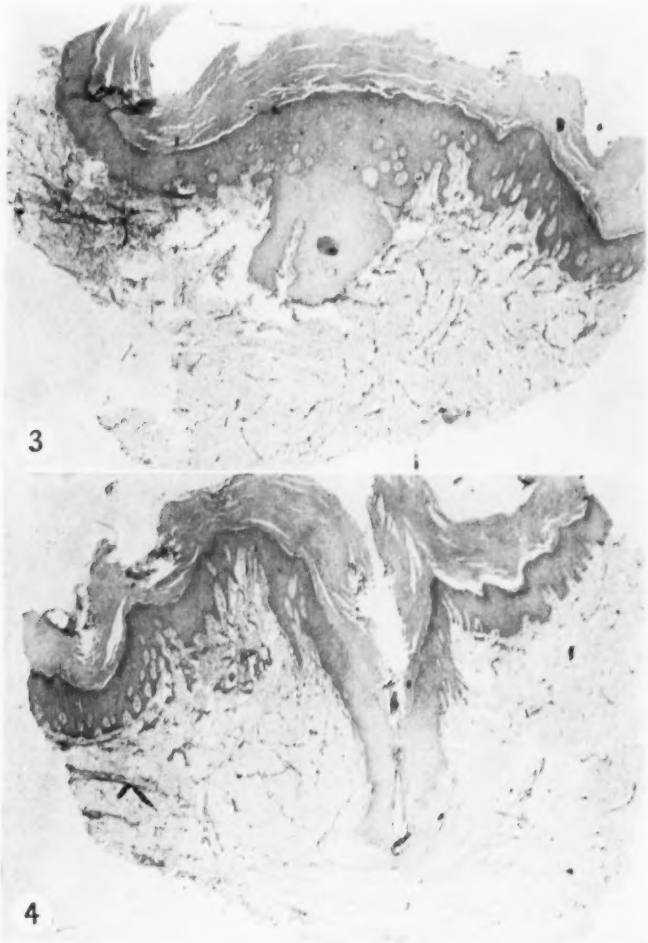

Fig. 3.—Hair imbedded in epidermis with focal hyperplasia of epidermis around hair; × 15.
Fig. 4.—Hair projecting through epidermis a short distance into dermis; × 15.

thickened epidermis, presumably due to desquamation of epidermal cells around the hairs, creating a pseudofollicle often lined by much keratin. These pseudofollicles usually contain hairs, although the hairs may have fallen out or been pulled out. They may be shallow or deep, and the deep ones form simple epithelial-lined sinus tracts. There is no definite evidence that these tracts tend to branch. From a tract

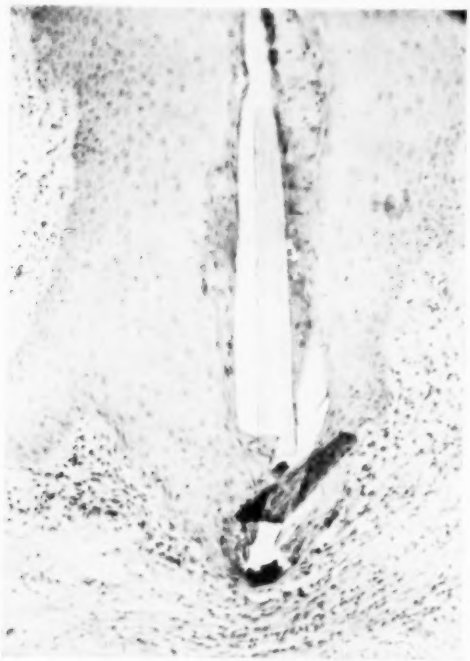

Fig. 5.—Higher magnification of Figure 4; × 150.

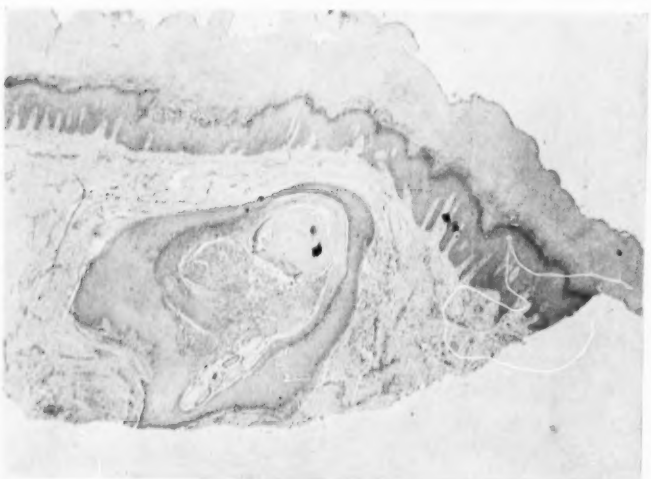

Fig. 6.—Cyst formed in dermis at end of pseudofollicle; × 15.

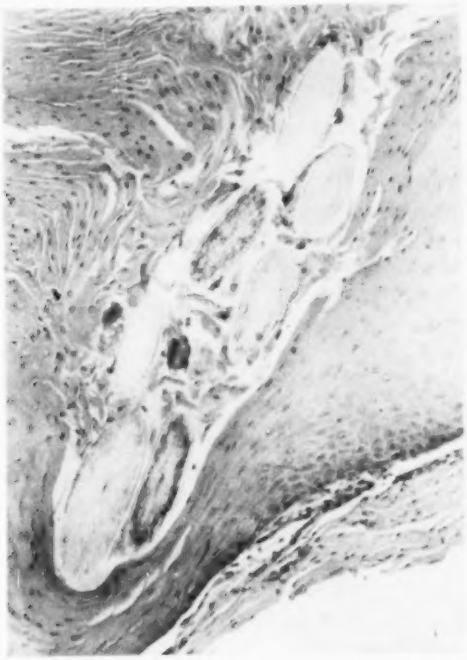

Fig. 7.—Higher magnification of cyst wall and contents shown in Figure 6. Note different colored hairs. × 150.

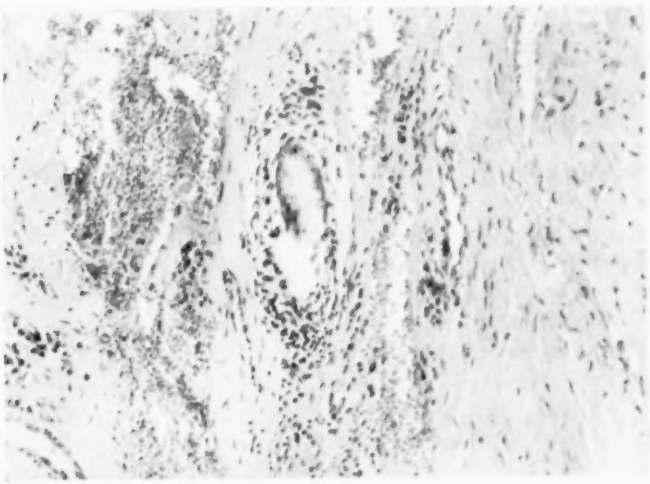

Fig. 8.—Foreign body reaction, chronic inflammation and scar tissue around hair in depths of dermis; × 150.

a cyst may be formed within the dermis or subcutaneous tissue, due to narrowing or complete closure of the upper portion of the tract (Figs. 6 and 7). With any of the above changes variable degrees of chronic inflammatory change may be seen in the adjacent dermis. Superimposed infection may convert the epithelial tract or tracts into inflamed branching and connecting sinuses. The destruction of the epithelial lining of the infected tracts allows the hairs to become surrounded by inflammatory tissue and foreign body reaction. Chronic draining sinuses may result, or healing with scar formation may occur spontaneously or following operative intervention. All the above changes except infected branching sinuses were demonstrated in tissue removed from the patient described, and the illustrative photomicrographs are taken of tissue removed from this patient. The infection had subsided by the time of the first tissue removal, and only the scarring and foreign body reaction around a portion of hair remaining deep in the tissue were seen (Fig. 8). Different colored hairs may often be seen in the lesions (Fig. 7).

PATHOGENESIS

Patey and Scarff [4] suggested that postanal pilonidal infections often start at the base of hair follicles. One of their cases with an interdigital lesion was stated to have

TABLE 2.—*Location*

	Interspace							
	L_1	L_2	L_3	L_4	R_1	R_2	R_3	R_4
Barbers examined	5	3	3	2	2	3	1	1
Cases from literature	0	0	5	0	1	2	3	1
Our case*	..	1	1	1	..	1	..	..
Total	5	4	9	3	3	6	4	2

* Two recurrent lesions not included.

a sinus leading into an epithelial-lined cavity which contained a hair follicle. Downing [5] was of the opinion that there were no hair follicles in the skin of the interdigital webs. In searching the literature, we could not be certain about this; so 30 specimens were taken from the interdigital webs of six adult male cadavers. Histologic study of these revealed no hair follicles. There were, of course, many sweat glands in this area.

Assuming that there are no hair follicles, from the appearance of the hair stubs removed from the lesions it would appear that the hairs are extraneous and somehow penetrate the epidermis directly—not through a follicle. Several barbers volunteered the information that they had more trouble with coarse hairs, which were stiffer. It can be shown that these stubbles are needle-sharp when clipped off obliquely to form a bevel. In their own voluble manner, several barbers offered interesting theories. One believed the condition started when the cloth was drawn between the fingers. Another suggested that it began when he used a vibrator which was held by stretching two long flexible coil spring straps over the middle three fingers. Many stated that hairs were often found embedded in the skin of the interdigital webs and also under the edge of the fingernail or cuticle. A female beautician said that she had pulled hairs from her feet and from the webs between her toes when she wore sandals at work.

In the pathogenesis of postanal pilonidal sinus, the "sucking action" of the gluteal fold is mentioned.[4] It might be postulated that a similar action occurs in the interdigital spaces, especially with the motion of the skin in manipulating scissors. The fact that it is a fold, where opposing surfaces of skin meet forcefully and repeatedly as in the gluteal fold, seems to us to be a factor in forcing the hairs into the skin once they have started. Unfortunately it was not tabulated how many of the affected barbers were left-handed or wore rings. It may be assumed that the majority, if not all were right-handed; of the 20 lesions found, 7 were on the right and 13 on the left. Of the 12 lesions in cases reported in the literature, 7 were on the right. In our complicated case, three of the four sites were on the left (two recurrent). Thus, out of 36 lesions, 15 were on the right hand (Table 2).

Nine of 36 lesions (those in the literature plus ours), occurred in the left third finger, six in the right second, and five in the left first interspace. How the barber grasps his instruments or wears a ring (usually on the left fourth finger) might thus conceivably play a part.

It might be considered that cleanliness and the manner and frequency of washing the hands play a part. In this respect, 71 barbers were examined in smaller shops (3 or fewer barbers), and 13 positive cases were found. Forty-four were examined in larger shops (four or more barbers), with only two positive cases (Table 1).

SUMMARY AND CONCLUSIONS

Interdigital pilonidal sinus is an occupational disease among barbers which is due to extraneous short hairs penetrating the skin and acting as foreign bodies.

The condition is usually benign but occasionally becomes disabling, as shown by a patient who developed six lesions in four interspaces, complicated by repeated infection and recurrence in surgical scars.

Of 115 barbers examined, 15 were found with lesions. Symptoms were minimal and in eight had gone unnoticed. Four had multiple lesions. The uncomplicated condition is described.

The structure of the lesions is variable. There may be an epithelial-lined tract or cyst or simply "dimpling" with or without penetration of the epidermis by the hairs. When the epidermis is penetrated completely, the hairs may remain free in the cutis, with a surrounding foreign body reaction.

The pathogenesis is discussed. As far as can be determined, there are no hair follicles normally in the skin of the interdigital webs. The exact mechanism of development of the lesion is not known, but several theories are offered.

ADDENDUM

Currie, Gibson, and Goodall (*Brit. J. Surg.* **41**:278-286 [Nov.] 1953) examined the hands of 77 male hairdressers from 18 barbershops and found 10 with interdigital sinuses. Inspection of 61 female hairdressers revealed no lesions. Two of their treated cases required skin grafts.

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INTRAMUSCULAR CHLORAMPHENICOL IN OUTPATIENT TREATMENT OF VENEREAL DISEASE

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IN PREVIOUS publications,* the reasons for preference of a parenteral antibiotic with a slow rate of absorption and effectiveness for many of the venereal diseases were summarized. Since the treatment of venereal disease has shifted to the outpatient clinic, the search for such a preparation has been intensified.

Harb,[1] in his original work on the pharmacology of intramuscular suspensions of powdered chloramphenicol given intramuscularly, noted the ease and dependability of administration, the lack of local and systemic reactions, and the development of therapeutic blood levels of the antibiotic for 72 to 96 hours when it is adequately administered in 4-gm. doses.

The preparation used in this study was a micronized powder of chloramphenicol supplied in 1- and 2-gm. vials † to which sterile saline or distilled water was added. In this study, injections of 4 gm. were given in a total volume of 8 ml. of suspension, forming an easily injected liquid.

In granuloma inguinale and lymphogranuloma venereum, when the course of chloramphenicol was to consist of three or more injections of 4 gm., it was arranged to provide a period of 72 to 96 hours between the injections. In four patients, one interval of 48 hours was permitted in the schedule in order that no delay in the treatment would be necessary when the 72- or 96-hour injection was to fall on a week end. In all of the latter patients the results were satisfactory, and it was felt that the slightly shortened schedule had no influence on the therapeutic results.

Approximately half of the patients receiving one or more injections complained of slight to moderate discomfort in the injected buttock when questioned. This lasted for a period of 6 to 48 hours. There was no instance of sterile abscess formation, induration, or prolonged pain at the site of injection.

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* References 1 and 2.

† Parke, Davis & Company, Detroit, supplied the chloramphenicol (Chloromycetin) for this study.

Special attention was directed to the possible effect of this therapy upon the blood.‡ In each of the patients receiving more than one injection of chloramphenicol, hemograms done during the post-treatment observation period showed no significant depression from previous values. In nine instances there was an improvement in the blood picture as the general condition improved after chloramphenicol therapy.

No instance of sensitivity, gastrointestinal symptoms, or systemic effects was seen in this series of patients.

DISEASES TREATED

Chloramphenicol has been reported effective in early syphilis § and in gonorrhea.‖ This paper deals with its further use in granuloma inguinale, chancroid, and lymphogranuloma venereum. In addition, 38 patients with nongonococcic urethritis were treated on the basis of a possible infectious etiology of the disease.

Results of Intramuscular Chloramphenicol Treatment of Granuloma Inguinale, Chancroid, and Lymphogranuloma Venereum

Disease	No. of Patients	Dosage of Chloramphenicol, Gm.	No. of Injections	Average Healing Time, Days	Comments
Granuloma inguinale	21	12	3	12.5	18 patients observed 3 to 12 mo.; 1 relapse re-treated with 14 gm. chloramphenicol with healing, 5 months' follow-up
	3	16	4	19.5	All healed; observed 6 or more mo.; extensive lesions
Total	24	..	..	13	23 healed; 1 relapse
Chancroid	20	4	1	9	Adequate healing with 1 injection
	14	8	2	12.2	Slow healing prior to 2d injection; rapid healing after 2d injection in 10 patients
	2	12	3	21	Extensive lymph node involvement
Total	36	..	..	11	Single injection not reliable; additional injections effective
Lymphogranuloma venereum	16	12	3	16	Bubos aspirated in 3 patients
	2	16	4	23.4	Extensive involvement; buboes aspirated
Total	18	..	..	17	

Granuloma Inguinale.—There were 24 patients treated with intramuscular chloramphenicol for granuloma inguinale (Table). The diagnosis in all patients was made by finding Donovan bodies in smears of the pathologic tissue. Twenty-one patients were given three injections of 4 gm. of chloramphenicol for a total of 12 gm., and 3 patients who had very extensive lesions (2 had large pseudobuboes) were given an additional 4-gm. injection for a total of 16 gm. All patients were observed biweekly until the lesion healed, then monthly for 3 months, and then at 6, 9, and 12 months. Eighteen patients have been observed six or more months, 21 have been observed three or more months, 2 patients (1 of whom is lost) have been observed two months, and 1, one month.

‡ References 3 and 4.

§ References 2 and 5.

‖ References 2, 6, and 7.

The lesions of six of the patients with small to moderate-sized lesions were completely epithelialized by the time the treatment was completed (six to seven days). The average healing time was 13 days. One patient, a 65-year-old Negro with an extensive cicatricial lesion, took 28 days for complete epithelialization, the longest interval in the series. There was one relapse—in a 30-year-old Negro who had a relatively small, 1-cm. lesion of the prepuce. This patient was then re-treated with 28 gm. of oxytetracycline and again relapsed. He had remained healed five months after re-treatment with 16 gm. of chloramphenicol given intramuscularly. Three patients in this series had received previous treatment elsewhere with oxytetracycline. Twenty-three patients have remained healed to date.

This series compares well with reported schedules in which other antibiotics were used,¶ giving probably a more rapid rate of healing than the others, with the possible exception of oxytetracycline, which gave comparable results in eight patients treated at the same clinic with a total of 25 gm., with one relapse.

Chancroid.—It has been our experience that oral treatment of chancroid often has proved unsatisfactory because of an excessive rate of treatment lapse and delinquency from observation as well as poor adherence of the patient to schedule. It was felt, therefore, that if a single effective injection could be used in the treatment of chancroid it would be very desirable.

Although chloramphenicol has been found to be not particularly effective when given orally for the treatment of chancroid, its intramuscular injection in a dosage of 4 gm. at the time of diagnosis would be a desirable method of treatment if it were found to be effective. No additional or adjunctive treatment was prescribed. The diagnosis of chancroid was based upon the clinical appearance of the lesions, a negative dark-field examination, and the Ducrey skin reaction. Smears, cultures, and bubo pus were studied at the Venereal Disease Research Laboratory. The Ducrey skin test was positive in 31 patients before treatment and in the remaining 5 became positive within 10 days after treatment was started.

After the initial injection of chloramphenicol, the lesion was observed for a week, and the injection was then repeated if there was no definite improvement during that time.

Results: Thirty-six patients were treated with chloramphenicol intramuscularly. In 20, the single injection was sufficient to completely epithelialize the lesions within 2 to 16 days (average 9 days). These, in general, represented patients with smaller lesions, although three had early inguinal buboes which healed without suppuration within 14 days. In the remaining 16 patients the lesion showed very little significant change, and an additional injection of 4 gm. of chloramphenicol was administered three to seven days after the first. Fourteen patients received two injections. Ten of these showed very rapid healing after the second injection and the remaining 4 healed more slowly. The total healing time in this group was 6 to 21 days, averaging 12.2 days.

The remaining two patients received a total of three injections. Both of these patients were women with bilateral buboes, and one had a large draining sinus. Both healed in 21 days.

Aspiration was necessary in one instance.

¶ References 1, 2, and 8 through 11.

Although a single injection cannot be considered reliable in the routine treatment of chancroid, this series compares favorably with that of 19 patients treated with sulfonamides, who healed in an average time of 12.6 days, and 18 patients treated with other antibiotics (oxytetracycline, streptomycin, chlortetracycline, and tetracycline), who healed in an average of 11.7 days. Chlortetracycline-treated patients showed superior healing, as has been noted elsewhere.[12]

Lymphogranuloma Venereum.—Oral and intramuscular administration of chloramphenicol has been found effective in the treatment of lymphogranuloma venereum,# but has been reported of less value than chlortetracycline.[10]

Eighteen patients with early lymphogranuloma venereum were treated with intramuscular injections of chloramphenicol in dosages of 4 gm. every 48 to 96 hours until a minimum of 12 gm. was given. Two patients with extensive fluctuating buboes received four injections (16 gm.). In no patient was chloramphenicol treatment extended over more than an 11-day period, and, except when aspiration of buboes became necessary, no other adjunctive treatment was given.

The diagnosis of lymphogranuloma venereum was based on the presence of a positive Frei skin reaction and/or positive complement fixation test in the presence of the clinical picture of inguinal lymphadenopathy with the "sign of the groove," with or without the history or presence of a primary lesion and constitutional symptoms. Patients with rectal strictures, chronic sinuses, or long-standing pathologic conditions were not included in this study.

All of the 18 patients had positive Frei reactions before, during, or after treatment. Buboes were present in all patients and were bilateral in six. In two patients with massive buboes, fluctuation occurred during treatment and aspiration became necessary. One patient with multiple fluctuant nodes and a sinus draining for two days was also included.

Results: After the first injection, systemic complaints, when present, usually disappeared within 24 hours, and the primary lesions healed within two days. There was little change in the character of the buboes for three to six days. In three patients the buboes continued to enlarge during this time. In 11 of the 18 patients fluctuation never occurred. Pain at the site of the buboes was relieved in from one to four days.

The interval of time necessary for complete healing, except for slight thickening of the inguinal tissue, which in some cases took a month or more to disappear, was 17 days. In the five patients in whom aspiration of the buboes was necessary, the healing time averaged 22.6 days.

Fifteen other patients were treated with 20 gm. of chlortetracycline. These showed an average time of 11.5 days for healing to occur. Aspiration was necessary in four of these patients. One patient was found to have relapsed or to have been reinfected at the time of his one-month follow-up. He was treated with 12 gm. of chloramphenicol, with healing in 13 days.

Nongonococcic Urethritis.—In an effort to determine the effect of a single injection of chloramphenicol in the treatment of nongonococcic urethritis, 38 patients with this diagnosis were treated with 4 gm. of chloramphenicol. The diagnosis was made when the patient presented a urethral discharge in the absence of positive

References 2 and 8.

smears and cultures for Neisseria gonorrhoeae. Each patient had received a previous injection of 600,000 units of procaine penicillin G in oil with 2% aluminum monostearate, in 10 instances for gonorrhea, at least seven days prior to the injection of chloramphenicol. Biweekly examinations were made, and, if no improvement was seen in one week, a second injection of chloramphenicol was given.

Although it was felt that a month's follow-up was desirable, there were only 26 patients who returned at that time. All patients were observed for two weeks or more after treatment. The criteria for "cure" were (1) freedom from any discharge for two weeks and (2) absence of other symptoms, such as dysuria or urethral itching or burning. The progress of any accompanying prostatitis was not closely followed. All patients were ordered to avoid alcohol and intercourse and not to "strip down" the urethra during the observation period.

Results: Thirty-eight patients were followed for at least two weeks after chloramphenicol treatment. All except five patients noticed some relief of their symptoms, and these five patients received a second injection without effect. Nineteen patients were considered completely relieved, the discharge and symptoms disappearing in an average of five and one-half days. Two additional patients noted relief within three days, but symptoms returned on the 10th and 11th day, respectively. Eleven patients were somewhat relieved but continued to have symptoms. Chloramphenicol was considered effective in half of this group of patients.

Thirty-five of a group of 42 patients treated with other medications were observed for two or more weeks after treatment. Eight of 10 patients (80%) treated with 10 gm. of oxytetracycline were completely relieved in an average of 3.4 days. The other two patients were not completely relieved.

Of 15 patients receiving three daily 1-gm. injections of streptomycin, 6 obtained complete relief in an average of 6.4 days (40% cure).

Ten patients were treated with 1,000 mg. of 11-dehydro-17-hydroxycorticosterone acetate orally over a seven-day period. Nine were followed for at least 21 days, and seven were followed for 40 days or more. One patient was relieved after five days. Although the discharge disappeared in two patients 16 and 22 days after treatment, it is doubtful that 11-dehydro-17-hydroxycorticosterone acetate was effective in these two patients.

SUMMARY AND CONCLUSIONS

Outpatient treatment of venereal diseases with one or more intramuscular injections of chloramphenicol is described.

Twenty-three of 24 patients with granuloma inguinale were effectively treated with 12 to 16 gm. of chloramphenicol. Half of 36 patients with chancroid were cured with one 4-gm. injection; additional injections were necessary to heal the remaining patients' lesions.

Seventeen of 18 patients with early lymphogranuloma venereum were cured, but with results considered inferior to those with chlortetracycline.

Chloramphenicol injections were effective in 50% of 38 patients with nongonococcic urethritis. Oxytetracycline was superior.

In nongonococcic urethritis, 11-dehydro-17-hydroxycorticosterone acetate was ineffective.

No toxic or sensitivity effects were seen.

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SPECIFIC TISSUE ALTERATION IN LEPROUS SKIN

VI. "Isopathic Phenomenon" Following BCG Vaccination in Leprous Patients

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IN THE skin of leprous patients a focal characteristic histological lesion developed at the site of injection of specific and nonspecific proteins. It was found that the injection of tuberculin, leishmanin, milk, and peptone elicited a lepromatous or pre-lepromatous structure characteristic of lepromatous leprosy.* The injection of these materials into the skin of normal persons elicited a nonspecific inflammation totally different from the lesion which developed in leprous patients. Lepromatous and pre-lepromatous structures were also noted to have developed in lepromatous leprosy patients at the site of insect bites and of erythema-nodosum-like eruptions appearing during chemotherapy.[3] These observations indicated that the skin of leprous patients has a specific altered reactivity.

A study of the reaction of leprous skin to living organisms was desirable. For several reasons BCG inoculation was selected. First, it has been reported that BCG inoculation might protect against infection with leprosy in healthy contacts. Second, it was desirable to find out whether BCG vaccination was capable of converting a negative lepromin test to positive in leprous patients, since it is generally accepted that a positive lepromin test is a favorable prognostic sign. Finally, BCG produces in healthy persons at the site of inoculation a specific and distinct lesion different from that seen in lepromatous leprosy. It was thus possible to distinguish histologically between the altered reactivity of the leprous patient and the lesion of BCG.

MATERIAL AND METHODS

BCG vaccine,† 0.1 ml., containing 0.025 mg. of dried bacilli or about 10^6 organisms, was injected intradermally over the left deltoid region. The inoculation was performed in 21 patients who suffered from lepromatous leprosy, 13 with and 8 without active skin lesions. The

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From the Department of Dermatology and Venereology (Dr. A. Dostrovsky, Director) and the Department of Pathology (Dr. H. Ungar, Director) of the Hebrew University-Hadassah Medical School, and the affiliated Hospital for Hansen's Disease of the Ministry of Health, Government of Israel.

* References 1 and 2.

† BCG vaccine from UNICEF (United Nations International Emergency Fund) was received through the courtesy of Dr. Ole Horwitz, of Denmark, who assisted in some of the vaccinations.

pertinent clinical and laboratory data of these patients are presented in the Table. All patients were receiving chemotherapy, and in four of them bacilli could no longer be detected in smears from the mucous membrane of the nose and from skin of the ear lobe.

Previous to the inoculation all patients were tested with tuberculin. For the tuberculin test, 1 tuberculin unit was used (PPD I, i. e., 1/50,000 mg. of International Standard Reference Preparation of PPD [Holm‡]). If the first test was negative, a second test was made with a dose of 10 tuberculin units (PPD II). Twelve patients were initially PPD negative before BCG vaccination, and of these eight became positive after inoculation.

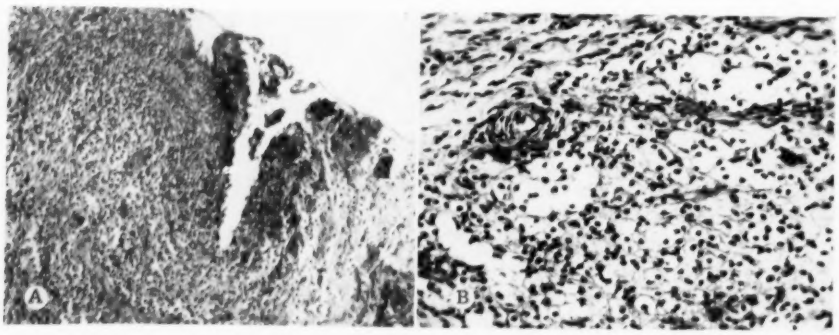

Fig. 1.—Leproma-like reaction, 3+, two weeks after BCG vaccination in a leprous patient. *A*, large ulcer with a base of fibrin and leucocytes covers a large aggregate of foam cells. Hematoxylin and eosin stain; × 92. *B*, the granulomatous tissue is composed of foam cells containing one large or many small vacuoles. A few lymphocytes are scattered among the foam cells. Hematoxylin and eosin stain; × 257.

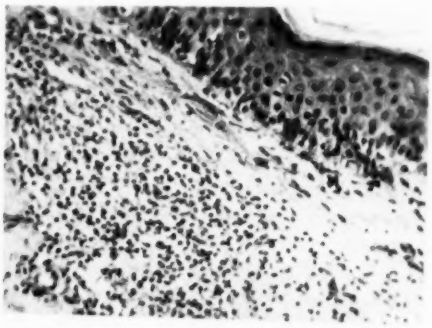

Fig. 2.—Leproma-like reaction, 3+, six months after BCG vaccination in a leprous patient. Focus of foam cells in the subpapillary layer of the cutis, separated from the epidermis by a zone free of infiltrations. Hematoxylin and eosin stain; × 290.

It is important to emphasize that the leprous patients reacted clinically to BCG inoculation as normal persons without leprosy. Those who were tuberculin negative before vaccination developed a lesion at the vaccination site as described in normal healthy persons without tuberculosis. Those who were tuberculin positive before vaccination exhibited clinically an accelerated reaction that corresponded to a Koch phenomenon.§ In three of the patients from the tuberculin-positive group a lepra reaction appeared.

‡ References 4 and 5.

§ References 6 to 8.

The lepromin test [9] was negative in all patients prior to the BCG vaccination. It was repeated three months and one to two years after the BCG inoculation.‖

Twenty-five biopsy specimens of the BCG inoculation sites were taken from 16 of the 21 patients, at intervals of from four days to 10 months after vaccination. The biopsy specimens were fixed in 10% formalin or Zenker's fluid. Paraffin sections were stained with hematoxylin-eosin, Van Gieson's, Weigert's elastica, and Ziehl-Neelsen's stain as modified by Putt.[10] At the time of biopsy, smears were taken from the floor of the biopsy wound and stained by the Ziehl-Neelsen method.

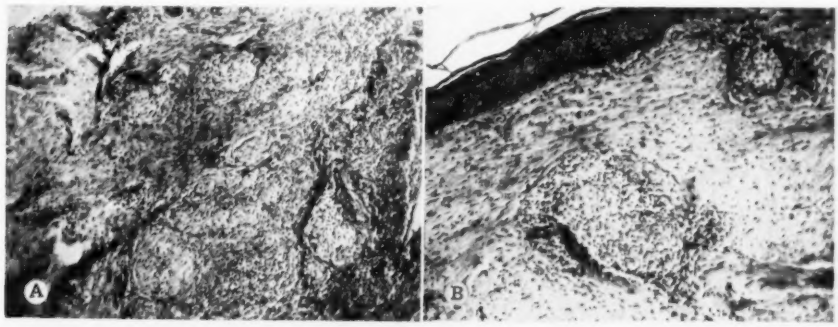

Fig. 3.—*A*, leproma-like reaction, 3+, five months after BCG vaccination in a leprous patient. Varying-sized focal granulomas, composed of foam cells, are demarcated from an extensive aggregate of foam cells. Hematoxylin and eosin stain; × 60. *B*, another case, six months after BCG vaccination. Sharply demarcated foci of granulomatous tissue scattered in the scarred cutis. Hematoxylin and eosin stain; × 86.

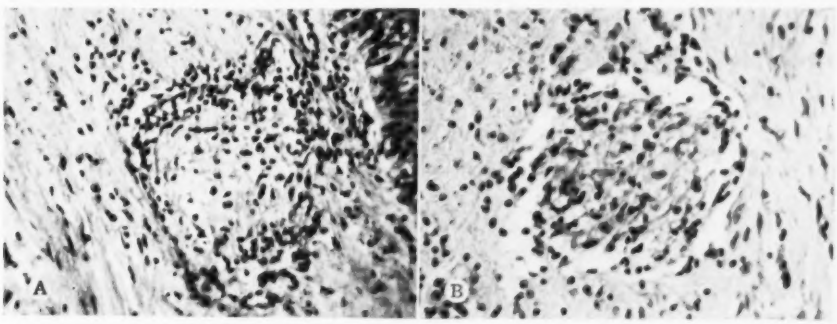

Fig. 4.—*A*, leproma-like reaction. Same as Figure *3B*. Foam cell granuloma slightly resembles a tubercle in its pattern. In contrast to a tubercle, however, the center is built up of foam cells containing vacuoles in their cytoplasm and of a few histiocytic cells with elongated nuclei. The periphery is composed of a rim of lymphocytes. Hematoxylin and eosin stain; × 215. *B*, another granuloma composed of foam cells and histiocytic elements in the center, surrounded by a rim of foam cells with a single large vacuole. Hematoxylin and eosin stain; × 258.

Controls.—For control purposes 13 biopsy specimens of the BCG inoculation site were taken from nine healthy persons 2 to 15 years of age, 2 to 12 months after inoculation. All were negative to tuberculin before BCG was given.

‖ One of the antigens used was received from Dr. R. S. Guinto through the courtesy of Dr. H. H. Wade, of the Philippines.

RESULTS

The intradermal injection of BCG into lepromatous patients elicited a histological reaction characteristic of leprosy. The lesions thus produced were the same in both tuberculin-negative and tuberculin-positive patients. The skin reactions were graded histologically according to a previous classification.[2]

In 17 of 25 biopsy specimens removed from the leprous patients there was found a leproma-like reaction (3+), consisting of granulomatous structures composed predominantly of foam cells (Figs. 1 and 2). The 3+ response elicited by BCG was essentially the same two weeks to six months after vaccination.

In four of these 3+ reactions taken five to six months after vaccination an additional feature was found. Within the extensive foam cell aggregates were seen foci clearly demarcated by the arrangement and composition of their cellular elements (Figs. 3 and 4). In these foci foamy cells containing several small or one large vacuole were arranged concentrically. Lymphocytes often formed a thin rim of cells

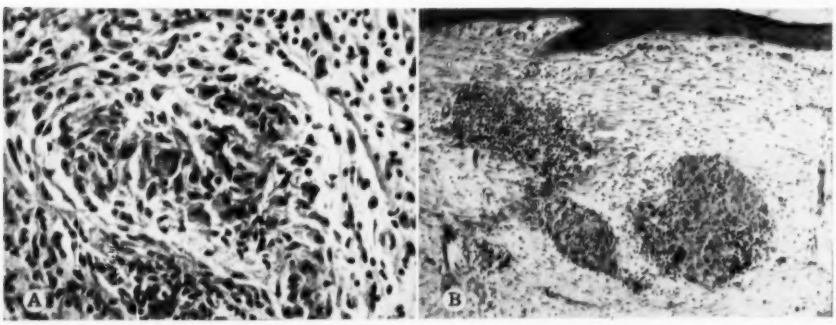

Fig. 5.—Control Case. *A*, tuberculous granulation tissue, four months after BCG vaccination in a nonleprous child, previously negative to tuberculin. No foam cells are present. Compare with Figures 3 and 4. Hematoxylin and eosin stain; × 229. *B*, the tubercle is sharply demarcated, composed of epithelioid cells, giant cells, and lymphocytes lying in a scarred dermis. Compare with Figure 3*B*. Hematoxylin and eosin stain; × 77.

at the outer borders of the focus (Figs. 4*A* and *B*). The appearance of these foci resembled a focal granuloma within a large aggregate of foam cells.

Bacteriological studies of these 17 specimens which were 3+ are recorded in the Table.

Prelepromatous reactions (2+) were found in three biopsy specimens taken four days to 10 months after vaccination. The prelepromatous reaction was characterized by smaller foci of foam cells situated around subpapillary blood vessels and around skin appendages of the deeper cutis.

Foam-cell nests (1+) were noted in two specimens removed two months and six and one-half months after BCG inoculation.

Three of the 25 biopsy specimens revealed no lesion characteristic of leprosy. One of these showed nonspecific granulation tissue two and one-half months after vaccination. The other two specimens were taken from vaccination scars and histologically exhibited dense collagen and scattered lymphocytes.

Clinical and Laboratory Data							Results							
					Smears		PPD				Acid-Fast Bacilli		Lepromin Test	
													Before BCG Vaccination	After BCG Vaccination
Name	Sex	Age	Clinical Type of Leprosy	Duration of Leprosy, Yr.	Nasal Mucous Membrane	Ear Lobe	Before BCG Vaccination	After BCG Vaccination	Interval Between BCG Vaccination and Biopsy	Biopsy Result	Smears from Biopsy Ground	Histol. Section		2-3 Months	1-2 Years
R. F.	F	33	A.l.l.	7	++	+++	+	+	4 days	++	Neg.	+++	—	+ MR	—
									r—16 days	+++	Neg.	+	..	.....	..
L. A.	F	24	A.l.l.	10	—	++++	—	+	16 days	+++	+	+++	—	+ FR	—
									r—10 mo.	++	Neg.	Neg.	..	.....	..
R. A.	F	31	I.l.l.	18	—	+	—	+	4 wk.	+++	Neg.	+	—	+ FR	—
S. V.	F	17	I.l.l.	1	+++	+	—	—	2 mo.	++	+	G	—	— MR	—
									r—6½ mo.	+	Neg.	Neg.	..	.....	..
S. S.	F	25	A.l.l.	5	+	+++	—	—	2 mo.	+++	Neg.	Neg.	—	+ FR	—
									r—5½ mo.	+++	0	Neg.	..	.....	..
E. F.	M	24	A.l.l.	13	G	+++	+	+	2 wk.	+++	G.	Neg.	—	— MR	—
									r—3¾ mo.	+++	++	+	..	.....	..
									r—6 mo.	+++	Neg.	Neg.	..	.....	..
C. R.	M	44	A.l.l.	21	+	+++	+	+	2 wk.	+++	Neg.	G.	—	— MR	..
C. N.	M	18	A.l.l.	12	+++	+++	+	+	2 wk.	+++	++	+	—	— MR	..
									r—2 mo.	+	G.	+	..	.....	..
M. K.	M	44	I.l.l.	27	—	—	+	Not done	2 wk.	+++	Neg.	Neg.	—	Not done	..
J. K.	M	20	A.l.l.	1	+++	+++	—	+	3½ mo.	+++	G.	Neg.	—	— MR	..
J. J.	M	20	I.l.l.	6	—	—	+	Not done	2 mo.	+++	0	Neg.	—	+ MR	..
									r—4 mo.	Scar unspec.	Neg.	Neg.	..	.....	..
G. S.	M	22	A.l.l.	3	+++	+++	+	+	5 mo.	+++	++	Neg.	—	— MR	—
S. R.	M	30	A.l.l.	17	+++	+++	—	+	5 mo.	+++	Neg.	Neg.	—	— MR	..
M. S.	M	38	I.l.l.	24	+	+	+	+	2½ mo.	Scar unspec.	Neg.	Neg.	—	+ MR	—
M. S.	F	19	A.l.l.	2	+	+++	+	+	2½ mo.	Unspec. infl.	0	Neg.	—	++ FR	—
									r—6 mo.	+++	Neg.	Neg.	..	.....	..
M. A.	M	23	A.l.l.	?	++++	++++	—	+	6 mo.	+++	++	++	—	— MR	..
A. M.	F	30	I.l.l.	2	—	—	—	..	Biopsy not done		....	....	—	++ MR	—
M. J.	M	31	A.l.l.	20	+	++++	—	—	Biopsy not done		....	....	—	— MR	..
M. P.	M	23	A.l.l.	8	+++	+++	—	+	Biopsy not done		....	....	—	+ FR	—
A. L.	F	55	I.l.l.	35	—	—	—	+	Biopsy not done		....	....	—	+ MR	—
S. P.	F	38	I.l.l.	?	+	+	—	+	Biopsy not done		....	....	—	+ FR	—

Explanations: Clinical type of leprosy: A.l.l.—active lepromatous leprosy; I.l.l.—inactive lepromatous leprosy.
Biopsy result: + foam cell nests; ++ prelepromatous reaction; +++ leproma-like granuloma; r—repeated biopsy.
Bacillary findings: G—acid-fast granules.
Lepromin test: MR—Mitsuda reaction (3 weeks); FR—Fernandez reaction (48 hours).

Controls.—Of 13 biopsy specimens taken from nine healthy persons inoculated with BCG, seven revealed a histological reaction characteristic of tuberculosis (Fig. 5).

In three lesions nonspecific inflammation and fibrosis were found, and in three biopsies of vaccination scars collagen fibers and scattered lymphocytes were noted.

LEPROMIN TEST

The Table presents the data of the lepromin tests. Previous to BCG vaccination all the leprous patients were lepromin negative. Two to three months after BCG inoculation 11 of 20 patients tested were lepromin positive at 48 hours (+ to ++), and 5 of the 11 were also positive at three weeks. One to two years after BCG vaccination, all patients were again lepromin negative.

COMMENT

By "isopathic phenomenon" is meant the histological response characteristic of the host's specific altered tissue reactivity elicited by a specific living organism. The skin of leprous patients displayed this phenomenon. The injection of BCG elicited a lesion characteristic of leprosy and not of tuberculosis. Positive or negative tuberculin or lepromin tests did not alter the lepromatous response induced by BCG. Nor was time a factor, since the characteristic histological lesion was obtained four days to 10 months after BCG inoculation.

The specificity of the isopathic phenomenon was illustrated by the histological response obtained in the skin of healthy subjects following BCG inoculation. In these instances BCG elicited a lesion identical with that of tuberculosis. Foam cells such as were found in leprosy were never seen in these cases.

These observations showed some similarity to Koebner's isomorphic phenomenon. In contrast, however, to this phenomenon which is provoked by a nonspecific irritation, the leproma-like reaction in leprous skin was caused by living BCG bacilli.

The isopathic phenomenon appears to have been found in only one other condition, sarcoidosis. Lemming [11] described the appearance of a sarcoid plaque following BCG vaccination in a patient with sarcoidosis. Leider and Sulzberger [7] and Leider and Hyman [12] found that the clinical and histological lesion elicited by BCG in sarcoidosis resembled sarcoid tubercles. Putkonen,[13] Warfringe,[14] Bjørnstad,[15] Schaumann and Seeberg,[16] and Nelson [17] noted sarcoid lesions in sarcoid patients following the injection of Kveim antigen, virulent and killed tubercle bacilli, killed BCG bacilli, tuberculin, and homogenates of human spleen.

The results of the present investigation provoked several problems. Does the inoculation of BCG produce tuberculosis in the leprous patient or does it merely activate the leprosy at the site of injection? From the clinical aspect, BCG vaccination resulted in tuberculosis in leprous patients. Those that were tuberculin negative became tuberculin positive after vaccination and those that were positive before BCG injection showed an accelerated reaction at the site of inoculation (Koch phenomenon). From the histological aspect, however, the lesion elicited by BCG vaccination was a lepromatous or prelepromatous structure. There were four cases in which focal granulomas were seen among foam-cell aggregates. One other case developed scattered Langhans giant cells in the induced lepromatous reaction. But these varia-

tions were not characteristic of tuberculosis. The dilemma remained in that clinically the leprous patient reacted as if the body had tuberculosis but histologically he responded with a lepromatous lesion.

The question was also raised whether the injection of BCG in suspected leprous cases would reveal the presence of active leprosy. If the leprous patient characteristically develops a lepromatous or prelepromatous structure at the site of BCG vaccination, it would be possible to detect early cases by this method. As an extension of this, vaccination might be of value in determining the effectiveness of treatment. Several observations seemed to indicate that after intensive and effective chemotherapy the characteristic lesion did not develop at the site of BCG inoculation.

The present investigation did not throw much light on the benefit of a lepromin-positive reaction in leprosy. Tisseuil [18] proposed BCG vaccination as a preventive measure in 1928. Fernandez [19] showed that a lepromin-negative reaction in normal persons could be converted to a lepromin-positive reaction by BCG vaccination. He suggested that BCG inoculation be used to protect lepromin-negative persons exposed to leprosy, on the assumption that a lepromin-positive reaction signified resistance to leprous infection. Montestruc and Blaché [20] have reported that BCG vaccination performed in children of leprous parents soon after birth protected them from the disease while they lived with their leprous parents. None acquired leprosy up to a period of 12 years. Some of the other children, without BCG inoculation, living under similar conditions, developed the disease. This problem is now being intensively studied by leprologists throughout the world.¶

In the present study 11 of the initially lepromin-negative patients were converted to weakly positive reactors two to three months after BCG vaccination. All were negative again when retested one to two years later. Similar observations were recently reported by Convit and co-workers.[33]

SUMMARY

At the site of BCG injection into the skin of leprous patients a granulomatous lesion developed histologically which was characteristic of leprosy and not of tuberculosis. Clinically the leprous patients reacted to BCG vaccination as normal persons without leprosy.

The histological development of a granuloma characteristic of the host's altered tissue in response to injected living specific organisms has been designated an "isopathic phenomenon."

The isopathic phenomenon was present in 22 of 25 biopsy specimens taken from 16 leprous patients. It appeared as early as four days and was found 10 months after BCG inoculation.

Thirteen biopsy specimens were taken from the BCG inoculation site in nine healthy children who were tuberculin-negative before vaccination. In seven, granulomatous lesions developed characteristic of tuberculosis. In the remaining six specimens nonspecific inflammation or scar tissue was found.

It was suggested that the isopathic phenomenon may be used to detect leprosy in contacts and to determine the effectiveness of chemotherapy against the disease.

In this study Dr. J. D. Feldman gave advice and help; photographic work was done by Mrs. H. Weinman and Miss P. Aslan.

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MONILIASIS COMPLICATING ANTIBIOTIC THERAPY

Clinical and Laboratory Studies

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THE INCREASED incidence of local and systemic moniliasis since 1946 is evidenced by the frequency of published reports during the past seven and one-half years. A number of investigators have implied that the antibiotic drugs are causative agents in the genesis of these mycotic infections. Textbooks on bacteriology [1] and recent publications generally accept Candida albicans as a common inhabitant of the skin, gastrointestinal tract, oral cavity, and the vagina. Zimmerman,[2] Harris,[3] and others * state that the clinical manifestations of moniliasis which occur complicating antibiotic therapy are due to the destruction of the normal flora of the body, thereby removing the inhibiting effect of these organisms which compete with the co-existing C. albicans for nutritive substances in the same substrate. Leitner [7] and Harris [3] agree that alteration in vitamin biosynthesis may be a factor in lowering the resistance to the Candida, and they claim success in the prevention and treatment of monilial infections by the administration of vitamin B complex concurrently with the antibiotic drug.

Woods and his associates [4] believe that the suppression of Gram-negative and Gram-positive bacteria by these drugs allows the C. albicans to grow profusely. Zimmerman [2] also suggested that a contributing factor was the loss of a growth-restraining substance normally produced by the natural intestinal flora which was lacking owing to destruction of these bacteria by the antibiotics. Kligman [8] stated that the wide-spectrum antibiotics do not sterilize the mouth or gastrointestinal tract but bring about a suppression of susceptible organisms which is followed by a gradual regrowth of antibiotic-resistant organisms to replace the original flora, but this growth is only temporarily resident.

There is a difference of opinion as to the stimulating effect of the various antibiotics on the growth of C. albicans in vitro and in vivo. Zimmerman [2] believed that these drugs stimulate the growth of this fungus, whereas Woods and his co-workers [4] were convinced by their in vitro studies that the antibiotics do not enhance monilial growth. Moore [9] stated that dilute solutions of chlortetracycline had a stimulating effect on C. albicans by definitely increasing the perceptible growth of the culture

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* References 4, 5 and 6.

as compared with a control. Seligmann [10] recently demonstrated in animal studies that sublethal doses of C. albicans became highly lethal when mixed with chlortetracycline (Aureomycin). In Kligman's analysis of the investigative work done in this respect, he states that there is no convincing evidence that antibiotics really stimulate the growth of fungi.

Woodward,† commenting on his vast experience with all of the currently used antibiotics, has noted a marked increase in the incidence of clinical manifestations of moniliasis. He and his collaborators have cultured C. albicans from the stools of patients who had diarrhea resulting from anibiotic therapy; they also have had two fatal cases of systemic moniliasis. Harris [3] reported five cases of vulvovaginitis, one case of perianal eruption, two of black hairy tongue, and one of diarrhea following antibiotic therapy, and he claimed to have cultured C. albicans from all of these. In Moore's experience,[9] cases of black tongue, cheilitis, glossitis, perlèche, vaginitis, and gastrointestinal symptoms due to Candida following the use of antibiotics were common findings. Woods and his co-workers [4] published a series of 25 cases of various manifestations of moniliasis including diarrhea complicating antibiotic therapy from which they successfully cultured C. albicans. It was Kligman's [8] opinion that most of the reported instances of localized moniliasis are not actually cases of this disease, and the definitive requirements for establishing this diagnosis are often insufficiently appreciated. The isolation by direct smear of a culture of C. albicans from the mouth or stools of a person who has been receiving antibiotics is not sufficient evidence for a diagnosis of moniliasis, and therefore many cases of perlèche, black tongue, glossitis, eczematous eruptions, and diarrhea complicating, or appearing coincidental with, the administration of the antibiotics, may be due to vitamin deficiencies or some local irritative phenomenon and not to the specific fungus infection. Hauser and Rothman [11] believe that the development of severe moniliasis is due to lowered resistance to invasion of the C. albicans, because if the organism is transferred to a person with normal resistance a very superficial type of infection occurs. In our experience ‡ in the treatment of approximately 3,000 patients by oral administration of the antibiotics, only 2 patients developed mild clinical manifestations of monilial infection from which the organism was recovered by cultures. It is interesting to note that the vaginitis in both of these patients subsided soon after the antibiotic drug was discontinued. In addition to these two cases, several patients with moniliasis apparently complicating antibiotic therapy have been seen in consultation for other practitioners.

The recent incrimination of moniliasis as the cause of numerous adverse reactions to the antibiotics and the unfavorable publicity in the lay and medical press has unfortunately placed a stigma on these valuable medicaments which may not be merited. In view of the doubts which have been raised by Kligman [8] and the results of the studies conducted in our department, it is believed that many of the cases reported as localized moniliasis are not due primarily to C. albicans, but that this organism is merely present as a coincidental inhabitant. In order for moniliasis to develop, a person must have a lowered resistance or an increased sensitivity to invasion of C. albicans.

The following laboratory and clinical studies have been undertaken in order to attempt a clarification of this important problem.

† Woodward, T. E.: Personal communication to the author.

‡ References 12 and 13.

LABORATORY STUDIES

Incidence of C. Albicans in Normal Human Flora and Influence of Antibiotics.—The statement has been repeatedly made in textbooks and in recently published articles that C. albicans is a common inhabitant of the gastrointestinal tract, the vagina, the skin, and the oral cavity. In order to determine the incidence of this organism in the normal flora of the human body the following experiments were conducted. Stool cultures were made on 100 patients who had not received any of the antibiotics for at least three months prior to examination. These subjects were all hospitalized for various causes at the University hospital. A second series of 150 examinations were conducted on patients who had been under treatment with penicillin or one of the broad-spectrum antibiotics for from two to four weeks, and a third smaller series was conducted on patients both before and after antibiotic therapy. To learn the incidence of C. albicans in the vaginal flora, cultures were made from 100 pregnant women from the obstetrical outpatient service who had not received any antibiotic drug. A second series of cultures was made from the

TABLE 1.—*Incidence of C. Albicans in Stool Cultures*

Prior to Antibiotic Therapy			After 2 to 4 Weeks of Antibiotic Therapy			
No. Specimens	No. Positive for C. Albicans	Per Cent	Antibiotic	No. Specimens	No. Positive for C. Albicans	Per Cent
100	16	16	Chlortetracycline	30	5	16.6
			Penicillin	35	5	14.3
			Oxytetracycline	35	6	17.1
			Chloramphenicol	15	2	13.3
			Erythromycin	35	5	14.3
			Total	150	23	15.3

vaginal tracts of patients who had been under treatment with penicillin or one of the broad-spectrum antibiotics. A similar study was conducted on cultures from the oropharynx.

In earlier experiments, the profusion of organisms which grew on the media made the isolation and identification of C. albicans a tedious process, and the need for some special preparation was obvious. In order to overcome this, 50 mg. of oxytetracycline (Terramycin) was incorporated into each 20 cc. of standard Sabouraud's medium before slanting in large tubes. Earlier experiments indicated that this antibiotic did not stimulate or retard the growth of fungi but did inhibit the growth of Staphylococci and Streptococci. After the specimen was inoculated and the tube labeled, it was incubated at room temperature and examined at daily intervals for growth. At the end of two weeks if no growth had occurred, the tube was discarded; however, if a growth appeared, a transfer culture was made on corn meal agar for positive identification of C. albicans.

Results of Stool Cultures (Table 1): One hundred specimens were obtained from patients who had received no antibiotic therapy for at least three months; of these, 16 were positive for C. albicans. The presence of this organism was established by transfer cultures on corn meal agar. Specimens were studied from 150 patients who had received penicillin or one of the broad-spectrum antibiotics and of these 23 (15.3%) were positive for C. albicans. Although the series on each of

the antibiotic drugs was small, it apparently made little difference in the percentage of positive results, as 16.6% of those receiving chlortetracycline (Aureomycin) were positive for C. albicans, 14.3% of those receiving penicillin, 17.1% of those receiving oxytetracycline, 13.3% of those receiving chloramphenical (Chloromycetin), and 14.3% of those receiving erythromycin. Stool examinations were performed on 25 patients before and after receiving oxytetracycline, and also on 25 before and after receiving erythromycin, but the incidence of C. albicans remained the same, and the administration of the antibiotic did not produce any variation in the percentage of positive results. In specimens of stool from persons who suffered diarrhea as a complication of antibiotic therapy the same percentage of positive and negative results for growth of C. albicans was obtained.

TABLE 2.—*Incidence of C. Albicans in Vaginal Flora*

Prior to Antibiotic Therapy		After 2 to 4 Weeks of Antibiotic Therapy			
No. Specimens	No. Positive for C. Albicans	Antibiotic	No. Specimens	No. Positive for C. Albicans	Per Cent
100	15	Penicillin	15	2	13.3
		Oxytetracycline	35	5	14.3
		Erythromycin	35	5	14.3
		Total	85	12	14.1

TABLE 3.—*Incidence of C. Albicans in Oropharynx*

Prior to Antibiotic Therapy		After 2 to 4 Weeks of Antibiotic Therapy			
No. Specimens	No. Positive for C. Albicans	Antibiotic	No. Specimens	No. Positive for C. Albicans	Per Cent
100	14	Penicillin	30	4	13.3
		Oxytetracycline	35	5	14.3
		Erythromycin	35	5	14.3
		Total	100	14	14

Results of Vaginal Cultures (Table 2): Cultures on specially prepared Sabouraud's media were made from the vaginal tracts of 100 pregnant women who had received no antibiotic therapy for a period of three months, and of these 15 were positive for C. albicans. Eighty-five specimens obtained from women who had received penicillin or one of the broad-spectrum antibiotics for periods of from two to four weeks revealed that 14.1% were positive for C. albicans. The administration of the antibiotic drugs apparently does not affect the incidence of positive results from the vaginal tract.

Results of Cultures from the Oropharynx (Table 3): Cultures from the oropharynx on specially prepared Sabouraud's media were made from 100 patients who had received no antibiotic therapy for at least three months, and of these 16 were positive for C. albicans. A similar study was performed on 100 patients who had been receiving penicillin or one of the broad-spectrum antibiotics for two to four weeks, and 16% of these had positive results. Administration of antibiotic therapy did not affect the incidence of the organism.

Effect of Antibiotics on Growth of C. Albicans in Media.—To determine at first hand the effect of antibiotics on the growth of C. albicans in media and to verify the previously published reports,§ preparations were made of oxytetracycline, chlortetracycline, penicillin, erythromycin, and chloramphenicol in Sabouraud's medium. Six Petri dishes were prepared as follows:

1. Control—plain Sabouraud's medium
2. 50,000 units of penicillin incorporated into Sabouraud's medium
3. 50 mg. oxytetracycline incorporated into Sabouraud's medium
4. 50 mg. chlortetracycline incorporated into Sabouraud's medium
5. 50 mg. chloramphenicol incorporated into Sabouraud's medium
6. 50 mg. erythromycin incorporated into Sabouraud's medium

A 24-hour culture of C. albicans in nutrient broth was prepared, and 0.2 cc. of this was inoculated onto the surface of each plate. The preparations were incubated at room temperature for 72 hours and a colony count was performed, with the following results:

1. Control 1,206
2. Penicillin 1,117
3. Oxytetracycline ...1,316
4. Chlortetracycline ..1,254
5. Chloramphenicol ..1,112
6. Erythromycin 1,371

This study supports the conclusions of Woods and his associates,[4] who used the quantitative method of measuring sediment of monilial growth in calibrated vaccine tubes. The antibiotics used in this experiment do not suppress or stimulate the growth of C. albicans on artificial media.

Effect of Coexisting Organisms on Growth of C. Albicans.—Conflicting statements as to the nature of action of the antibiotic drugs in the production of the clinical symptoms of moniliasis has stimulated the study of the action of other organisms on the growth of C. albicans in artificial media. This experiment was conducted to determine whether organisms, which are a part of the normal human flora, produce a growth-restraining substance which checks the production of moniliasis, or whether these organisms compete with the co-existing C. albicans for nutritive substances. Nine Petri dishes containing nutrient agar were inoculated with 0.2 cc. of an 18-hour culture of C. albicans in nutrient broth. This was carefully spread over the entire surface of the plate and allowed to incubate at room temperature for 12 hours. At the end of this time, a single streak of a 12-hour culture of one of the following organisms was made across the diameter of the plate:

Plate No.	Organism	Source
1	E. coli	Stock
2	E. coli	Autopsy
3	E. coli	Autopsy
4	E. coli	U. Pa.
5	A. aerogenes	Autopsy
6	S. albus	H.D.
7	S. aureus	Hordeolum
8	S. aureus	Autopsy
9	C. albicans (control)	U.S.P.H.S.

§ References 2, 4, 9, and 10.

In order to simulate natural conditions these preparations were incubated at 37 C. and read in 24 hours and daily thereafter. The single streak of the inoculated organisms grew profusely in the presence of the culture of C. albicans, and there was no evidence of any zone of inhibition, which denoted the lack of production of an inhibitor substance. In succeeding weeks the other organisms overwhelmed the C. albicans by their growth. It is apparent from this study that the organisms which normally inhabit the body restrain the growth of C. albicans by their overwhelming ability to utilize the nutritive substances present.

REPORT OF CASES

CASE 1.—This 4-year-old white girl was admitted to St. Agnes Hospital on Oct. 1, 1952, with a history of illness of two and one-half years' duration. At the age of 18 months, she had been admitted to a hospital in her home town because of acute tracheobronchitis, and in view of severe respiratory distress a tracheotomy was performed. Cultures were not made and the cause of the infection was not determined, but she was immediately started on penicillin injections. About a week after treatment was initiated, a reddish area appeared about the tracheotomy wound, and a short time later a reddish lesion appeared on the arms and legs. The physician suspected a penicillin reaction and discontinued this drug and substituted chlortetracycline. After this whitish patches appeared in the mouth, and the child developed a productive cough. The drug was changed to chloramphenicol, but no change was noted in the condition except a spread of the eruption to other parts of the body including the skin of the abdomen and the scalp. Oxytetracycline was administered but produced no change in the general condition. This period of treatment covered one and one-half years during which horns had developed on the nose, fingers, and legs.

Physical Examination.—A poorly nourished child of 4 years, small for her age, is in respiratory distress, coughing at frequent intervals with the production of a profuse mucoid sputum. There is a thick yellowish crust throughout the entire scalp, and the hair is greatly thinned. At the hairline, the margin of the eruption is sharply defined and bright pink. The face is pale; there are scaling lesions on both cheeks, and a large horn on the tip of the nose. On the chest and abdomen there are large well-defined, pink to bright red plaques covered with an adherent dry scale. Similar large lesions are present on the thighs. The legs are greatly thickened, owing partially to the large crusts adherent to the surface, and there is marked edema of the feet. On all of the toes there are varying degrees of horn formation. The arms and forearms are similarly affected. There is crust formation in the external canals of both ears and in the nostrils. The tongue and buccal mucosa are covered with a thick whitish membrane which is not easily removed. This membrane extends to the pharynx. The excursion of the chest is limited, and on auscultation large rhonchi were heard. The heart sounds were normal. No abnormality was elicited on examination of the abdomen.

Laboratory Studies.—Urinalysis: Reaction alkaline; specific gravity 1.016; trace of albumin; negative for sugar; no red or white blood cells; no casts. Blood Picture: Hemoglobin 9.6 gm. (63%), red blood cells 3,460,000, white blood cells 6,400.

X-ray Examination of Chest: There was a patchy infiltration throughout both lungs, due to a chronic infectious process consistent with the diagnosis of pulmonary moniliasis. (Repeated examination two weeks later showed no change.)

Bacteriological Studies: Cultures were made of the exudate from the throat, nose, skin, and fecal matter on Sabouraud's media. Mucoid colonies suggestive of C. albicans developed, and these were transferred to corn meal agar where the diagnosis was confirmed.

Course in the Hospital.—She remained in the hospital for two weeks; when she was discharged at the request of her parents little beneficial change had been noted except for slight improvement in her respiratory symptoms, which may be attributed to the administration by areosol of 1% sodium proprionate solution. The parents have continued this therapy at home, and, according to their observations, her appetite has improved and her cough is reduced in intensity. Our observations on her last visit to Baltimore in July, 1953, show no change over the original visit.

CASE 2.—A white boy aged 11, complained of soreness of fingers of eight months' duration. The mother said the infection made its appearance gradually on the second and third fingers of his right hand and involved only the distal phalanges in that portion surrounding the nails. She used various home remedies but produced no improvement. The family physician administered penicillin by injection; two weeks later the swelling increased greatly and an exudate developed. Therapy was discontinued, and the mother resumed treating the hands herself with hot boric acid soaks; improvement was noted, but the lesions did not completely resolve. Three months later he developed pneumonia and was treated with penicillin. A week after this treatment was initiated, the fingers swelled and the exudate returned. A culture of this pus was positive for C. albicans. Boric acid soaks followed by 5% methylrosaniline chloride in 50% alcohol produced a satisfactory result.

CASE 3.—A 50-year-old white business man was treated with chlortetracycline by his family physician for an acute upper respiratory infection, and the week following he developed severe pruritus ani. On examination he was found to have a partially defined scaly macular eruption surrounding the anus. Scrapings and cultures were made but were negative for fungi. A stool culture was positive for C. albicans. The patient was given two fractional doses of x-ray, 2.5% solution of phenol crystals in olive oil to apply locally and ¼ grain (0.014 gm.) tablets of phenobarbital three times daily. The lesions and symptoms subsided in two weeks, and there has been no recurrence.

CASE 4.—A 30-year-old white waitress and dishwasher developed severe paronychia involving all of the fingers on both hands. Without benefit of culture of the purulent exudate, she was given oxytetracycline, and the condition became much worse. One of my confreres (A. S.) cultured C. albicans from the discharge and applied hot boric acid soaks followed by 5% methylrosaniline chloride solution in 50% alcohol and produced a satisfactory result.

CASE 5.—A 44-year-old white woman, a meat handler, who had paronychia for 10 years, noted that the condition was much worse when she used soapy water. During this time she had received x-ray treatment, and various local applications from several physicians, without any success. She continued to have periods of remission and relapse. Recently she was given oxytetracycline and after a course of treatment lasting one week the condition involving the fingers became much worse and an exudate developed. A culture of this discharge was positive for C. albicans. She has shown marked improvement following applications of methylrosaniline chloride.

CASE 6.—A 38-year-old white dentist had paronychia limited to his right hand for the past four years. During this time he received x-ray treatment, ultraviolet light, and numerous local applications at the hands of several dermatologists and general practitioners. At the time of his first visit he had no discharge, and on the possibility that the eruption was bacterial, therapy with erythromycin was instituted, and the eruption became more severe. A purulent exudate developed, and scaling lesions appeared in his right palm. The antibiotic was discontinued and applications of methylrosaniline chloride were instituted. A week later symptoms had almost subsided. Three weeks later there was almost complete involution of the lesions.

CASE 7.—A 30-year-old white man developed elongation of the papillae and a dark brown discoloration of his tongue 10 days after beginning treatment with chlortetracycline for a severe upper respiratory infection. Cultures from the mouth and scrapings from the tongue were negative for C. albicans. Six weeks after therapy with chlortetracycline was discontinued, the patient's tongue resumed a normal appearance.

COMMENT ON CASE REPORTS

It is indeed unfortunate that the cause of the original respiratory infection in Case 1 was never discovered. Cases similar to this one were reported prior to the use of antibiotic drugs, and it is possible that this child had moniliasis antedating the administration of any of the antibiotics. There is a great possibility that the long-continued treatment with the various antibiotic drugs caused the condition to become severe and generalized, and although the mechanism of this adverse action is obscure, it was probably due to the removal of the inhibiting influences of the antibiotic-sensi-

tive organisms. The trend of events in this patient from the beginning of her illness to the present time should serve as an object lesson to internists and specialists in pulmonary diseases that the possibility of infection with C. albicans exists and cultures should be made on Sabouraud's media as well as on routine media prior to the institution of antibiotic therapy. This is especially true in chronic pulmonary disease.

In Case 2 the child obviously had a chronic paronychia due to C. albicans, and it may be assumed when the penicillin-sensitive organisms were destroyed by the antibiotic, the monilial infection progressed. Cases 4 and 5 present a similar picture following administration of oxytetracycline, and in Case 6 the reaction developed following administration of erythromycin. The same conclusions may be reached in all of these cases; that is, the antibiotics were not responsible for the production of moniliasis, because this condition was already present. Destruction of the inhibiting organisms by the antibiotic drugs was probably responsible for exaggerated clinical appearance.

The symptoms presented in Case 3 are typical of many such complaints reviewed by dermatologists. In this patient the existence of C. albicans was coincidental with the pruritus but was not the cause of the condition. Recovery in this patient was prompt after the antibiotics were discontinued, and there was no specific therapy directed against the presence of C. albicans. In this instance, the pruritus was due to sensitization to the drug and was not caused by any microorganism. The mere presence of C. albicans does not imply that it is producing symptoms. In Case 7, moderately severe hairy tongue developed after chlortetracycline therapy, but in this case as in many other similar patients who have not received antibiotics, it was impossible to grow any organism on the media. The cause of hairy tongue has not been determined to the satisfaction of the majority of dermatologists, and this entity was a common finding prior to the advent of the antibiotics. It is true that the incidence of this entity has increased since these drugs have enjoyed such popularity, but in our experience when the C. albicans has been cultured from these lesions, it has existed as a coincidental finding and not as the etiologic agent of the condition.

SUMMARY

The laboratory studies indicate that the antibiotics do not stimulate or retard the growth of C. albicans. The organism is present in the normal human flora in 14 to 16% of persons, as determined by cultures from the oropharynx, the stools, and the vagina. In vitro studies also indicate that the C. albicans growth will flourish when antibiotics are administered, because of the suppression of growth of organisms which normally utilize the nutritive substances in the body. In reviewing the trend of events in the cases reported in this paper and of a large series of cases observed but not reported, careful analysis of the histories presented suggests that these persons probably had clinical infection with C. albicans before any antibiotic drug was administered. Kligman [8] stated that the wide-spectrum antibiotics did not enhance the growth of C. albicans in vitro and did not potentiate the disease in animals with experimental moniliasis. The presence of this organism in the stools, vagina, or mouth of a patient suffering from diarrhea, pruritus ani or vulvi, or stomatitis, regardless of the severity does not justify a diagnosis of moniliasis. Some clinical evidence of the disease entity must be evidenced. Many of the reactions which have been reported as monilial infection complicating antibiotic therapy do not bear close

scrutiny and do not satisfy the critical requirements necessary to establish the diagnosis. This is especially true of the cases of stomatitis, black hairy tongue, and diarrhea. These may be expressions of sensitivity or a deficient nutritional state. The antibiotics are valuable adjuncts to the therapy of bacterial diseases, in many instances replacing some of our time-worn methods, and reports of possible adverse reactions should be carefully reviewed before publication. The recent appearance in the literature of many reports relative to the production of moniliasis by administration of these drugs and the warning issued by the Council on Pharmacy and Chemistry of the American Medical Association has given rise to a feeling of insecurity among many physicians when they contemplate the necessity for antibiotic therapy. It is quite possible that such warnings and reports are not justified, and, if so, rectification of this misinformation should be published for general medical consumption.

CONCLUSIONS

1. C. albicans may be found as part of the normal intestinal flora in 16% of normal persons. The incidence of this organism is not influenced by the administration of penicillin or the broad-spectrum antibiotics.

2. C. albicans may be cultured from the vaginal tracts of 15% of normal pregnant women. The incidence is not affected by antibiotic therapy.

3. C. albicans was found to be present in the oropharynx of 14% of normal persons. The incidence is not affected by antibiotic therapy.

4. Antibiotics do not stimulate or suppress the growth of C. albicans on artificial media.

5. Cultural studies indicate that organisms which normally inhabit the body restrain the growth of C. albicans by their overwhelming ability to utilize the nutritive substances present.

6. In the vast majority of instances of adverse reactions which have been attributed to moniliasis, C. albicans is present as a coincidental finding and not as the causative factor.

7. It is suggested that the development of moniliasis is due to lowered resistance to the invasion of C. albicans and not to antibiotic therapy. In cases of clinical moniliasis which have received antibiotic therapy, the increased severity of the condition is probably due to the suppression of organisms which normally utilize the nutritive substances, thereby allowing overgrowth of the C. albicans.

ABSTRACT OF DISCUSSION

GEORGE M. LEWIS, New York: This presentation represents much more work than might be immediately apparent to this audience. From the title one might assume that moniliasis is a frequent complication as the result of the administration of the broad-spectrum antibiotic drugs. However, I would deduce from this report of Dr. Robinson that he has serious doubts that this is so. He thus allies himself with Kligman and some others who prefer to consider the evidence incomplete and who believe that the apparent increase in moniliasis may be due in part to faulty diagnosis. It should be stated that most observers believe the incidence of moniliasis is increased after the administration of these drugs. This presentation is a serious attempt to resolve the matter, but at this time it would probably be well to keep an open mind. Particularly in regard to elderly patients, the experience of most physicians indicates a vulnerability following administration of chlortetracycline and oxytetracycline not only with the tendency to develop lesions of localized moniliasis but also with a distinct possibility of systemic dissemination with increasing

age. Contrary to Robinson, I do not believe that this yeast-like organism is a common inhabitant of the intact skin or of the vagina. It is our experience that C. albicans is often found in the gastrointestinal tract of adults, the incidence increasing with age. At age 50, the percentage approaches 100 (*New York J. Med.* **37**:878 [May 1] 1937; **38**:859 [June 1] 1938). I should be interested to know whether Dr. Robinson found this to be the case in his series. Another factor in this problem which is often overlooked is the increased virulence sometimes assumed by C. albicans, which explains epidemics of perlèche such as Finnerud reported. However C. albicans usually requires some definite breakdown in immunity before it is pathogenic.

The thesis that administration of antibiotics causes moniliasis de novo seems fantastic, and I did not know that a vigorous denial, such as Robinson makes, was necessary. It always seemed more logical, and I thought was so accepted, that the broad-spectrum antibiotics produced their effect either by a growth-stimulating effect on C. albicans in the gastrointestinal tract or elsewhere in the body or by killing off other microorganisms which had a restraining influence on C. albicans. Robinson has attempted the difficult task of interpreting the literature in the light of his own observations. It is perhaps well to again state that one must guard against interpreting too rigidly the results of in vitro tests. I would personally place most importance on the case histories in which he reports clinical reactions after administration of the broad-spectrum antibiotics, and agree with his belief that the reason for this is probably due to coincidental destruction of competing microorganisms. I am sure Robinson would hesitate to hold up the broad spectrum antibiotic drugs as innocuous, simply because all of the reactions to them may be something besides a fungous disease. Particularly in elderly people, the broad-spectrum antibiotics should be used with due caution at all times and only for good reason in the presence of existing moniliasis.

Dr. Everett R. Seale, Houston, Texas: Dr. Robinson is to be commended on the presentation of data which is quite timely. I heartily agree with him in that there has been no increase in cutaneous moniliasis during the wide-spectrum antibiotic era. We reviewed the records of 6,000 consecutive patients observed from Jan. 1, 1946, to July 1, 1947, and a corresponding number of records of patients seen during the last 18 months and found the incidence of intertriginous moniliasis and monilial paronychia during the two periods to be exactly the same. Chlortetracycline and oxytetracycline have been employed in a large series of cases of acne over a prolonged period. There have been no monilial complications. We observed, as did Livingood and his group, a few incidences of moniliasis following the topical application of neomycin to intertriginous sites, particularly when it was used in an aqueous solution over an extended period. On the other hand, we have not noted this complication after application of neomycin hydrocortisone for perianal itching. We have seen only two cases of clinical thrush following the ingestion of wide-spectrum antibiotics and one of these was a case of lupus erythematosus in the terminal phase of the disease.

Undoubtedly oral and perianal irritation may occur after the ingestion of some antibiotics, and in some cases C. albicans can be demonstrated by direct examination and culture, but the clinical picture of a yeast infection is lacking and in such patients the lesions clear without the use of specific medication. Certainly some persons are more susceptible to yeast infections than others, and with our practice being, in the main, an ambulatory one, we would expect to see fewer complications from any cause than would occur in a more debilitated group of hospital patients.

I do think, and this is borne out in the literature, that organisms of low pathogenicity may become more virulent if their normal antagonists are suppressed by antibiotics. Dr. Ellard Yow of our Department of Medicine, Baylor University, has reported 56 cases of Proteus and Pseudomonas infections following the prolonged use of antibiotics. Most of his patients were persons with chronic diseases. However, in an experiment conducted in the same manner as Dr. Robinson's, there was no increase in the number of patients showing these organisms in their stools after the administration of wide-spectrum antibiotics. It seems to me a far more serious matter is the development of antibiotic-resistant strains of Staphylococci and Streptococci.

One word concerning treatment of moniliasis and particularly the intertriginous type. We have found methylrosaniline chloride in 1 or 2% strength irritating and have followed the sug-

gestion of Conant Calloway and our associates and employed this drug in 1 to 4,000 and 1 to 8,000 aqueous solution in the acute phase of the disease, with most gratifying results. If bacterial infection is also present, neomycin in 1 to 1,000 dilution is included in the methylrosaniline chloride solution. If the process is not too acute or extensive, half-strength Castellani's paint without basic fuchsin has proved to be the best remedy.

Dr. Clarence S. Livingood, Detroit: I have only one brief comment to the effect that it seems pertinent to call attention to the fact that the administration of the broad-spectrum antibioics (especially chlortetracycline) to seriously ill and/or debilitated patients may result in the development of what seems to be an acute severe enteritis which may be fatal. This reaction seems to be more common in persons who have had extensive bowel surgery. Apparently, it is due to the emergence of highly virulent resistant strains of Staphylococci. If the complication is recognized, the administration of erythromycin may be life-saving, in that the organism is apt to be sensitive to this antibiotic.

As far as I know, serious and/or fatal reactions of this type have not followed short-term or prolonged administration of broad-spectrum antibiotics to patients with dermatological conditions such as acne vulgaris, dermatitis herpetiformis, and various types of cutaneous bacterial infections; it seems to occur or at least reach potentially fatal proportions only in patients who are debilitated and/or seriously ill, or in persons who have had bowel surgery. Nevertheless, this is one more reason for avoiding the indiscriminate use of this group of therapeutic agents.

Dr. Albert M. Kligman, Philadelphia: I think that we can say that the contest of opinion among those who hold varying factors to be responsible for these adverse reactions has produced a great deal of heat in this area and very little light.

What has really happened is that we have created, by antibiotic therapy, somehow or other, a new disease or a new disease complex. First, the *bête noir* that was supposed to explain everything was Candida invasion; it is interesting to see that the fashions are changing. Now the protagonists of the bacteria are gaining sway. Staphylococcus aureus, Proteus, and Pseudomonas and other organisms, some of which are not very virulent, are beginning to be inculpated in the origin of this disease complex.

I think that the crucial point of the whole discussion with regard to the role of bacteria and fungi in these complications is that persons who develop either a monilial infection or a superimposed bacterial infection, are, as Dr. Livingood has clearly pointed out, sick. They are people with depressed resistance. They are ill and have an increased susceptibility to organisms which are ordinarily not highly pathogenic. Many of them are preterminal. Surgical trauma, cachexia, or old age may operate to make such persons vulnerable. Rarely does one hear of relatively healthy persons developing a serious infection with antibiotic-resistant fungi and bacteria. It is too naive to say that the cause of death in a person with lymphatic leukemia, who has received chlortetracycline for two months and who subsequently has developed generalized moniliasis, is moniliasis. That isn't quite true. Moniliasis may have been the terminal event in that situation, but that person died of lymphatic leukemia.

We realize that it is becoming increasingly difficult to die of a bacterial disease. We have ways of preventing that and persons who have chronic debilitating and even lethal diseases have to find other ways to make their exit from this world, and one of the ways of doing that is to contract a fungus infection or an infection with some bacterial organism which has become abundant because of elimination of competitors. It should be stressed, at any rate, that fungus infections do occur after antibiotic therapy, but this development is usually explicable on the basis of decreased resistance. Furthermore, this complication is rare.

I would just like to leave this thought with you that we don't know what this constellation of side-reactions really is. Nobody knows. There is a multiplicity of symptoms, vaginitis, dermatitis, cheilitis, pruritus ani, gastroenteritis and stomatitis, and no one has presented a compelling account of their origin.

Dr. J. Lowry Miller, New York: I am one of those who feel that you do not see reactions after ingestion of broad-spectrum antibiotics and that the Candida is always present. After listening to Dr. Robinson's remarks this morning, it occurred to me that the group in which this

reaction might occur are those in whom the Candida is already present as a harmless inhabitant. Dr. Robinson's results show that there was no increase in the percentage of patients showing Candida on stool culture after giving a broad-spectrum antibiotic over that in an average group of approximately the same age. Perhaps if we cultured for Candida before giving broad-spectrum antibiotics and gave these antibiotics only to the patients who were negative for Candida, we could eliminate the reactions which we now see.

Dr. Jacob H. Schwartz, Boston: I, too, in the main agree with Dr. Robinson, but I would like to side with Dr. Lewis in cautioning about the administration of the wide-spectrum antibiotics not only in the aged but also in the very young and those with debilitating conditions.

Dr. Lewis Kane of Boston has done a good deal of work with antibiotics and has seen systemic moniliasis with fatality and also generalized cutaneous and mucous membrane moniliasis following long-term administration of the wide-spectrum antibiotics. These patients have not had clinical moniliasis that could be detected before the administration of the antibiotics.

I feel that the administration of vitamin B complex together with the broad-spectrum antibiotics might be of value in lessening the incidence of a complication.

One word about the incidence of C. albicans in the vagina. I am interested in that particular phase and am studying the incidence in young women, married women, and pregnant women in various phases. Dr. Robinson, unless I misunderstood him, mentioned pregnant women. In the series of cases I have studied and in those reported, there is an increase of C. albicans in the vagina of pregnant women, and, like Dr. Lewis, I feel that in the normal vagina, that is, that of nonpregnant women, the incidence of C. albicans is rather low.

Dr. Harry M. Robinson Jr., Baltimore: I would like to take this opportunity to thank Dr. Lewis, Dr. Seale, and the others who discussed my paper for the suggestions they have made for continued studies on this subject.

Our confreres in medicine, the internists, are primarily responsible for causing so much of the confusion that now exists. Every time a person who receives one of the antibiotics develops diarrhea, if stool cultures are positive for C. albicans, this organism is held to be responsible for the reaction. The mere presence of this organism does not prove it to be the causative factor.

Both Dr. Lewis and Dr. Swartz have raised a very important problem—that is, the long-continued administration of antibiotics in the aged. I think that in these persons the reason for the development of moniliasis is lowered resistance to invasion. The elderly diabetic woman with vulvitis, from which I cultured C. albicans, certainly would not be a candidate for antibiotic therapy.

We must bear in mind, without too severe criticism, the plight of the general practitioner. When he is called to see a patient who has pneumonia or severe upper respiratory infection, or someone who has an elevated temperature and is quite ill, he must utilize some therapeutic procedure. There has been so much written about the specificity of antibiotics for such infections that he is prone to employ such drugs.

I am against the administration of antibiotics in patients with ulcerative colitis. I think that Dr. Livingood raised a very important point. Several deaths have occurred from moniliasis, and whether or not these persons had clinical moniliasis before they received the antibiotics is a question which I cannot answer.

The women whom I observed in my original studies on incidence of C. albicans were between the ages of 18 and 40 years. I used pregnant females primarily because of the claims by the obstetricians concerning the high percentage of moniliasis they observe in their patients. My findings indicate 16% to have positive reactions; therefore I am not in agreement with them.

The antibiotics are not innocuous drugs; they are potentially dangerous and should be used with caution. In previous publications I have stated that before antibiotic drugs are used, specific indication for their employment should exist. We have had four deaths from penicillin therapy at the University Hospital, and none of the four patients who received this drug should ever have received it in the first place. Two of those patients were over 60 and were being treated for late latent syphilis. They died, not from moniliasis, but from severe bullous erythema multiforme.

I hope I have been able to answer all the questions that were asked, and I thank you again.

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PATHOLOGIC PHYSIOLOGY OF STASIS SYNDROME

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COMPLICATIONS associated with varicose veins are important because of their frequent occurrence and the disability and suffering which they cause. Approximately 10 to 17% of the population have varicose veins,[1] 75% of all varices occur before the age of 30. After the second decade, varices occur four times as often in women as in men.

The chief complications of varicose veins are of great economic importance because of their frequency in the adult age group. In the United States, it is conservatively estimated that there are 300,000 to 400,000 people with stasis leg ulcers.[2] The objective complications of varicose veins include edema, pigmentation, eczema, cellulitis, phlebitis, cutaneous sclerosis, and frank ulceration.[3] These complications have as a common denominator chronic venous insufficiency. Any one or a combination of these changes may occur in a lifetime, depending on the effectiveness of appropriate therapy.

The term "stasis syndrome" is used to imply a condition of chronic venous insufficiency producing cutaneous and subcutaneous changes, ranging from edema to ulceration. The purpose of this report is to correlate the pathologic physiology and symptomatology of the stasis syndrome.

ANATOMY OF THE VEINS OF THE LOWER EXTREMITY

The veins of the lower extremity consist of three main systems: the superficial, the deep, and the communicating veins. The superficial system consists of a long, or internal, and a short, or external, saphenous vein and their numerous tributaries. These lie for the most part beneath the skin in subcutaneous tissues from which they receive little external support. The deep system consists of main channels through which blood returns to the large veins of the trunk, i. e., the common femoral, the superficial femoral, deep femoral, and popliteal veins in the thigh and below the knee, the posterior and anterior tibial, and the perineal vessels. All the above-mentioned veins normally contain segmentally arranged bicuspid valves that permit the blood to flow only to the heart. The communicating veins in the thigh connecting the femoral and the long saphenous vein are relatively few in number; however, many

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occur in the lower leg joining the deep and the superficial systems. All the communicating veins contain bicuspid valves which permit blood in normal extremities to flow only from the superficial veins to the deep ones.[2]

DEFINITION OF TERMS

Varicose.—Varicose, derived from Greek, means dilated. Varicose veins are of two types, primary and secondary. Primary varicose veins develop spontaneously, and in 43% [4] of all patients with primary varices there is a hereditary history of varicose veins. Secondary varicose veins develop after venous obstruction, the most common cause being an ileofemoral thrombophlebitis.[3]

The Peripheral Venous Heart.[5]—By this is meant the interplay between the intrinsic leg muscles and the segments of vein between competent valves. By this mechanism venous blood is returned to the heart, the peripheral venous heart serving as a true blood pump so long as the valves of the veins are competent.

Post-Thrombotic Syndrome.[6]—In this syndrome, there are alterations in all four components of the circulatory system. The arterial, venous, lymphatic, and capillary systems undergo pathologic physiologic changes. The term implies changes in the skin and subcutaneous tissues which occur after thrombosis of one of the veins of the lower extremities.

MECHANISMS

In the normal circulation of the lower extremities, the blood flows through the arteries into the capillaries and is returned to the heart by way of the veins. Venous return depends upon hydrostatic capillary pressure, the action of the intrinsic muscles of the leg, the state of the venous valves, and changes in intrathoracic pressure associated with movements of the diaphragm.[7] The most important factor in venous return is the action of the intrinsic muscles of the leg. The external pressure they exert against the venous wall forces blood flow in the direction allowed by the valves, i. e., towards the heart. When the pressure is released, the competent valve prevents regurgitation of blood from above, and the segment of vein can fill only from below. A useful term to define this interplay is the so-called "peripheral venous heart."

Any condition which alters the normal action of the venous valves may result in a syndrome referred to as "venous insufficiency." Whether there is congenital absence of the valve leaflets, fibrosis and atrophy of the leaflets, or mechanical incompetency caused by dilatation of the vein wall, the result is reflux of venous blood.

There are two main types of varicose veins.[8] The primary type develops spontaneously (congenital absence of valves, congenital weakness of vein wall) [8]; the secondary type develops after venous obstruction or increased pressure within the vein from internal or external causes. The usual cause of secondary varices is a deep thrombophlebitis. After organization and canalization of the thrombus, the valves are left incompetent and fibrotic.[9] This results in inefficiency of the deep veins which normally return 80 to 90% of the venous flow from the leg.[1] A result of this is an increased flow of blood and an increase of pressure on the superficial veins. The superficial system responds to this with dilatation of the vein wall (varicosities.)[7] The occurrence of varices in pregnancy is an example of external pressure producing mechanical interference with venous return. In secondary varices, whatever the etiology, there is a common disturbance, i. e., increased hydrostatic pressure with subsequent dilatation and incompetency of the valves.

CONSEQUENCES OF VARICES

The complications secondary to varicose veins are edema, pigmentation, eczema, chronic indurated cellulitis, recurrent thrombophlebitis, ulceration, and elephantiasis (lymphedema).

PATHOLOGIC PHYSIOLOGY

Normal Capillary Function.—The capillary is the most important unit of the circulatory system. It is here that fluid and metabolic exchange takes place between the blood and tissue spaces. In normal circulation the capillary hydrostatic pressure is 46 cm. of water at the arterial end of the capillary. This is significantly greater than the 36 cm. of water pressure exerted by the colloid osmotic force of the plasma.[5] The differential causes a flow of fluid into the tissue spaces. At the venous end of the capillary the hydrostatic pressure is 16 cm. of water. The greater pressure of the plasma draws fluid into the venular end of the capillary.[10] Under normal conditions the capillary loses an insignificant amount of protein (96% efficient) [11] (Fig. 1).

Disturbed Capillary Function.—A change in the hydrostatic pressure in the capillary or in the colloid osmotic pressure may disturb the usual exchange of fluid.

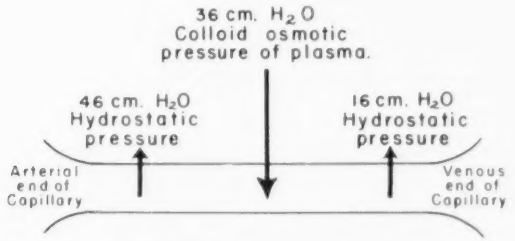

Fig. 1.—Diagrammatic illustration of circulatory dynamics in normal capillary.

With the formation of varicosities, there is an increase in the hydrostatic pressure of the veins. With an increase in capillary pressure fluid filtration into the tissues increases proportionally. Under these conditions the capillary loses large amounts of protein.[11] The lymphatics are unable to resorb the large amounts of fluid and protein. Because of this, effective osmotic pressure of the plasma is lowered, resulting in an even greater filtration into the tissue spaces.

Lymphatic circulation may be profoundly altered if the venous pressure remains persistently elevated (as in chronic indurated cellulitis). Another factor in the formation of edema is anoxemia of the capillary wall. This is thought by some [12] to occur in chronic venous insufficiency.

Edema.—This is frequently the earliest sign of venous disease. Swelling of the ankles or lower legs occurs at first after physical activity and disappears on bed rest. The formation of edema, which is simply increased fluid in the tissues, is mainly the result of increased hydrostatic pressure in the capillary,[13] with fluid and protein entering the tissue spaces.

In the edematous phase there is microscopic evidence of dilated lymph spaces and separation and swelling of collagen bundles (Fig. 2).

Pigmentation.—In the early stages of chronic venous insufficiency, pigmentary changes occur either before, during, or after the edematous phase. The clinical appearance of the stasis pigmentation is distinctive. Patchy areas of brown discolor-

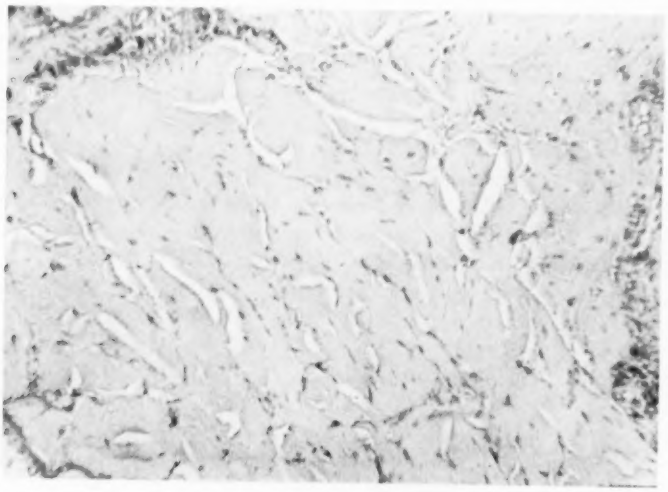

Fig. 2.—Photomicrograph illustrating separation and swelling of collagen bundles in the cutis with edema spaces; × 130.

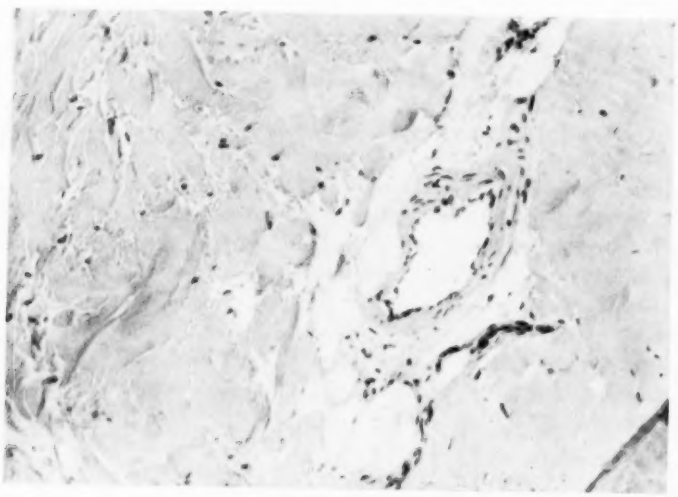

Fig. 3.—Dilated atonic venule and the dense sclerotic collagen. Photomicrograph of cutis from patient with chronic indurated cellulitis; × 130.

ation lie over varices. As the pigmentation progresses, there may be large coalescing patches extending around the ankles and at times encircling the lower legs. Purpuric and petechial lesions are frequently present, owing to increased capillary fragility. (Fig. 3).[14]

Owing to the great increase in hydrostatic pressure in the capillary bed, trauma to the lower legs or ankles results in rupture of the capillary wall with the extravasation of erythrocytes into the cutis.

The microscopic findings in this stage consist of dilated capillaries congested with erythrocytes; some capillaries have ruptured, and free erythrocytes are present in the cutis. Pigment granules are deposited throughout the cutis. These granules are composed of hemosiderin and stain blue with potassium ferrocyanide (Pearl stain) (Fig. 3).

Stasis Eczema.—Eczema occurs around the ankles and lower legs in many patients with chronic venous insufficiency. Clinically, it may be dry and scaling, vesicular, or exudative. The pathogenesis of this eczema is unknown. Factors such as edema, hypoxia, and poor nutrition, combined with scratching and trauma, are to be considered of pathogenetic significance.*

Histologically, stasis dermatitis is divided into acute, subacute, and chronic stages. In acute stasis dermatitis, the microscopic picture is that of an acute dermatitis with edema, crusting, and acanthosis. In chronic stasis dermatitis there is hyperkeratosis and pronounced acanthosis; the corium is fibrotic with varying degrees of atrophy of the dermal appendages. A nonspecific inflammatory reaction is scattered throughout the cutis, and large amounts of hemosiderin produce brown pigmentation. The arteriole may be thick walled, and dilated capillaries in the upper cutis as well as occasional thickening of the veins may be noted.[16]

In cases of acute stasis eczema, particularly those in which there is secondary infection or in which injudicious topical therapy has been applied, an acute weeping dermatitis involving the entire leg and frequently spreading to the trunk and arms may occur. This phenomenon is known as autoeczematization. Studies by Cormia and Esplin [17] have demonstrated that the antigen responsible is derived from the epidermal cells of the primary dermatitis. These workers note the epidermal antigen may act as a complete antigen or possibly may be derived from a combination of bacterial products or other substances to form a combined antigen. Their experiments suggest that the antigen is transported from the primary eczematous sites by the leucocytes.

Microscopically, the autoeczematization dermatitis is that of a nonspecific subacute or acute dermatitis.

Chronic Indurated Cellulitis.—This condition occurs in cases of long-standing stasis disease. It is clinically characterized by a brawny induration of the tissues with a periodic low-grade inflammatory process. In cases of persistently elevated venous pressure, the walls and valves of the lymphatic vessels become thickened and there is perilymphatic fibrosis producing irreversible changes.[12] This fibrosis is probably associated with edema fluid containing a high protein content which has been found to provoke fibrous tissue proliferation.[18] The fibrotic tissue is periodically involved in a low-grade inflammatory process secondary to the excoriations and eczematous changes in the epidermis. When the inflammatory process clears, the tissues are left in a brawny fibrotic state, and occasionally deposits of calcium are left in the sclerotic areas.

* References 14 and 15.

Microscopically, there is little change in the epidermis. The changes in the cutis consist of (1) diffuse homogenization of the collagen, (2) fragmentation or absence of elastic tissue, and (3) blood vessel changes in the cutis which show thickening and partial occlusion of the arterioles. Occasionally small spicules of calcium are

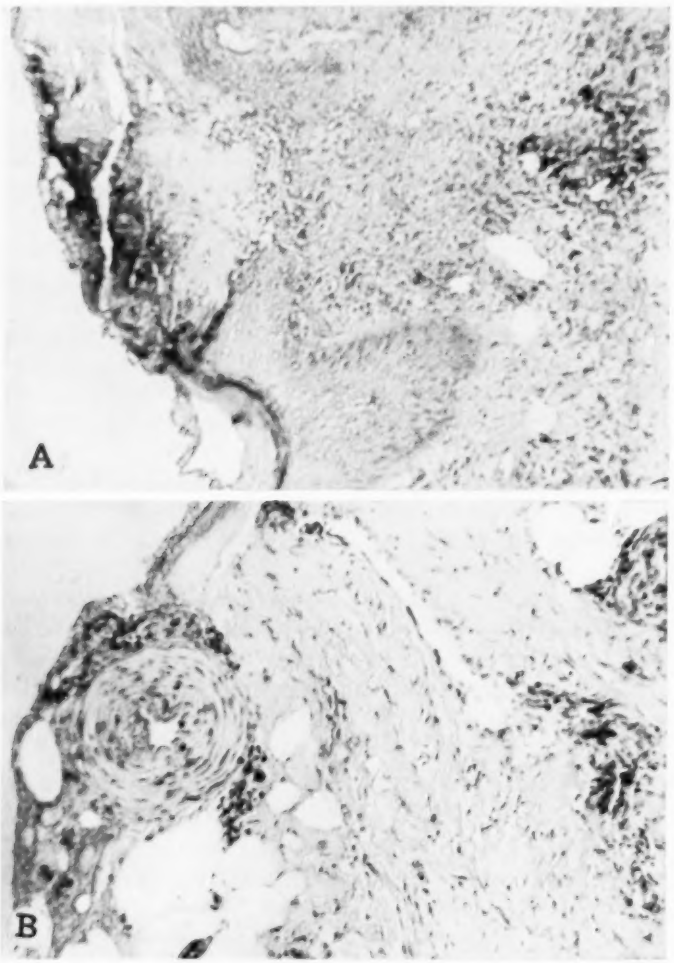

Fig. 4.—*A*, Photomicrograph of early stasis ulcer showing destruction of the epidermis, edematous changes in the cutis, and cellular infiltration; × 130. *B*, Thickened arteriole in the lower cutis. Biopsy from same patient as *A* with stasis edema and ulcer; × 130.

observed. In general, the picture is that of marked sclerosis apparently secondary to avascularity. There is atrophy of the dermal appendages (Fig. 4 *A* and *B*).

Ulceration.—Ulceration occurs first in the areas of greatest devitalization, the most common site of which lies around the malleoli because the communicating veins in this region receive little support from the tendons through which they

pass.[6] The ulceration may begin secondary to trauma or possibly from the breakdown of the devitalized tissue.

Clinically, the ulcer usually has an irregular soft margin. The base may be infected and odorous. The skin adjacent to the ulcer is often hyperpigmented and sclerotic. Occasionally a dilated ("feeder") vein is noted extending into the ulcerated area.

Microscopically, the area around the ulcer may show the changes of stasis eczema or chronic indurated cellulitis. The epidermis at the border of the ulcer often shows pseudoepitheliomatous hyperplasia with thickening and irregularity of the rete malpighii. The surface of the ulcer is covered with an exudate of serum, fibrin, and cellular debris. The base is edematous, with many dilated newly formed capillaries. There is an infiltrate consisting of small round cells with varying num-

Fig. 5.—Photomicrograph of vein from patient with thrombophlebitis. Note the organization and recanalization in the thrombus. Van Gieson's plastin stain; × 20.

bers of polymorphonuclear cells. Extravasated erythrocytes may be noted in some areas. The deep cutis has a fibrotic pattern, with atrophy of the dermal appendages. There is relative ischemia due to destruction of lymphatics and occluded arterioles.

An ulcer may be defined as a localized area of necrosis. Because of hypertension in the capillaries, sclerosis of lymphatics, alterations in collagen, and hypoxia in the cutis, the affected tissues leave little recuperative ability. These irreversible tissue changes in and around the ulcer account for the poor healing or chronicity of the lesion (Fig. 5).

LYMPHEDEMA

Lymphedema is commonly associated with chronic venous insufficiency. The lymphatics of the lower extremity are damaged by the preexisting thrombotic state.[19] The walls and valves of the lymph channels are thickened; there is perilymphatic fibrosis and obstruction may occur.[18] The lymph channels suffer identically as the veins in the stasis syndrome. Lymphatic stasis may persist after venous stasis which

initiated it has been relieved. The patients with lymphedema suffer from repeated bouts of cellulitis and lymphangitis. Occasionally elephantiasis of the limb results.

The microscopic picture of lymphedema is characterized by the presence of numerous dilated lymph spaces (Fig. 2). Associated changes such as dilated capillaries and disturbance in the collagen are also present.

RECURRENT THROMBOPHLEBITIS

The sluggish flow in varices plus the presence of infection in the adjacent cutaneous areas predispose the patient to bouts of thrombophlebitis.[20] The superficial veins are usually affected. Clinically, involvement of the saphenous veins and superficial branches is characterized by tender, red, raised nodules in the skin or cord-like segments which follow the course of the vessel. Constitutional symptoms are mild.

Some cases are thought to be purely mechanical in origin. In these cases, no organisms or abscess formation are present. Other cases are found to be infectious in origin and positive cultures may be obtained. These cases may be complicated by abscess formation and breakdown, septic emboli, and toxemia.[5]

PATHOLOGY

Microscopically, the veins appear thick walled and have small lumina due to proliferation and fibrosis of the intima. There are usually organization and canalization of the thrombus and destruction or absence of the valve leaflets (Fig. 5).[9]

SUMMARY

In patients with chronic venous insufficiency, a state of ambulatory venous hypertension exists. This is reflected by inner hydrostatic pressure in the capillary bed, causing a loss of fluid as well as protein into the tissue spaces. The increased capillary pressure with rupture of capillaries produces pigmentary changes in the skin. Damaged lymphatics result in lymphedema and cutaneous sclerosis following cellulitis and lymphangitis. Continued damage to the cutis and subcutaneous tissue results in the formation of indolent ulcers.

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Clinical Notes, New Instruments and Techniques

COMPARATIVE INCIDENCE OF XANTHELASMA IN JEWS AND GENTILES

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During recent months, I have seen a large number of patients for removal of plaques of xanthelasma palpebrarum. The absence of specific methods of treatment and lack of general knowledge of the condition prompted a series of investigations which are still in progress. The present communication deals with the comparative incidence of the lesions in Jews and non-Jews of the same age groups, and some observations regarding cholesterol levels.

It was apparent from the start that the only constant observation was the significantly higher rate of occurrence of xanthelasma in the middle aged and elderly as compared to younger age groups. There is a general impression as to its higher incidence in Jews, but I find no statistical study recorded.

I first examined 347 elderly patients hospitalized in the chronic illness division of the Baltimore City Hospitals. Of these, only 14 showed xanthelasma plaques on one or both upper lids. In this group of 347 patients, there were only 2 Jews. This group was compared with 221 additional patients, all inmates of Levindale, a home for elderly Jews.

Only 4% of non-Jews, ranging in age from 50 to 104 years were affected, while more than four times as many (17.4%) Jews in a comparable age group exhibited plaques.

Xanthelasma has frequently been associated with diabetes mellitus. There is no significant difference in the incidence of diabetes mellitus in elderly Jews and non-Jews in these two groups of institutionalized people. However, almost half the Jewish diabetics had xanthelasma while none of the non-Jews was so affected.

Hypercholesterolemia is usually considered part of the picture of xanthelasma. Serum cholesterol levels in the non-Jews with or without xanthelasma averaged about 200 mg. per 100 cc. Cholesterol levels in the Jews were significantly higher, with a tendency toward even higher levels when xanthelasma was present. While the cholesterol determinations on these patients were done in the laboratories of the respective institutions, spot checks at random proved that the methods were comparable.

COMMENT

There is no apparent explanation for the extreme variations in incidence of xanthelasma noted in this study. It will be necessary to examine many more patients in selected racial and national groups to determine whether the difference in incidence is due to true hereditary factors or whether diet controls the incidence of xanthelasma.

SUMMARY AND CONCLUSION

1. Five hundred sixty-eight elderly institutionalized patients were examined to determine the incidence of xanthelasma.

2. Four per cent of the non-Jews examined had one or more plaques, while 17.4% of the Jews were affected.

3. The incidence of diabetes mellitus in these two groups of Jews and non-Jews is about the same. None of the diabetic non-Jews in this study was affected with xanthelasma, while 44% of the diabetic Jews showed one or more xanthelasma plaque.

From the Division of Dermatology, Medical Service of the Baltimore City Hospitals and the Johns Hopkins Hospital.

4. The average serum cholesterol level in middle-aged or elderly non-Jews was 200 mg. per 100 cc., but the average in Jews of the same age group was 300 mg. per 100 cc.

5. There was a significant elevation in cholesterol levels in Jews with xanthelasma. This was not noted in non-Jews.

6. The study should be continued on an expanded level, in order to determine the influence of race, diet, climate, and other factors on the incidence of xanthelasma.

Dr. Henry Nagel, Resident Physician at Levindale, cooperated in this study.

STILBAMIDINE IN TREATMENT OF WIDELY DISSEMINATED BLASTOMYCOSIS (WITH TWO-YEAR FOLLOW-UP)

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EVANSVILLE, IND.

Although a large number of therapeutic measures have been utilized through the years in attempts to control the lesions of disseminated blastomycosis, it is only recently that these efforts have been attended with success. The introduction of a group of compounds, the diamidines, into clinical use, has ushered in a new era in the control of deep mycotic infections.* Two cases of widespread blastomycosis have been treated with stilbamidine † (4,4'-stilbenedicarboxamidine) by me and are described below:

CASE 1.—A 38-year-old white man, employed as a rose grower. The first sign of illness was the appearance of two small, infiltrated, erythematous, 0.5 cm. by 0.8 cm. nodes on the left arm about Aug. 15, 1951. Shortly afterward, the patient was prostrated because of the onset of chills, fever, polyarthralgia, and bronchitis. He was hospitalized elsewhere, and biopsy specimens were obtained from the two nodes. In the meantime, his blood was found to have a positive agglutination for Brucella abortus, and a tentative diagnosis of brucellosis was made. Despite large doses of chlortetracycline (Aureomycin), chloramphenicol (Chloromycetin), streptomycin, and penicillin, he failed to improve. When first seen by me, he had intensely swollen knee joints, severe proctitis, and was running a spiking fever. Deep abscesses, 2 cm. by 3 cm., developed on the right foot and left hand, and these were incised and drained. Cultures of the pus from the abscess of the right foot were positive for Blastomyces dermatitides, and it was later determined that the material from the skin biopsies had contained B. dermatitides. X-rays of the right foot revealed evidence of osteomyelitis. The sputum was negative for fungi on direct examination and culture.

Stilbamidine treatment was initiated on Sept. 27, 1951, the first dose being 50 mg., which was administered intravenously in the last 100 cc. of a 500 cc., 5% dextrose infusion. This dose was repeated on the following two days. The daily dose was raised to 100 mg. on the next two days, and from Nov. 1 through Nov. 4, 1951, he received 150 mg. of stilbamidine daily. Treatment was resumed on Nov. 8, 1951, when he received 150 mg. Shortly after receiving this dose, he developed urticaria across the upper chest and back. This was controlled by the intramuscular injection of an antihistamine preparation. From Nov. 9 to Nov. 13, 1951, a daily dose of 150 mg. stilbamidine was administered and then treatment was suspended because of a temporary shortage of the drug. A considerable degree of nausea and vomiting developed during the course of the treatment, and at first there was a progressive loss of weight. However, there appeared to be a definite clinical improvement in other respects shortly after therapy was begun, and the swelling of the foot, ankle, and knees diminished. Treatment with stilbamidine was resumed on Nov. 19, and 150 mg. daily were given through Dec. 8, 1951. Clinical improvement continued slowly and, in addition, subsequent cultures showed a less luxuriant growth of the fungus. Stilbamidine was again administered in a daily dose of 100 mg. from Jan. 8 through Jan. 15, 1952. The total amount given was 5.85 gm.

* References 1 to 5.

† Stilbamidine was provided by Merck & Company, Inc., Rahway, N. J., and by the Wm. S. Merrell Company, Cincinnati.

This patient had a particularly stormy course during the major portion of his hospital stay and numerous supportive measures were necessary. Multiple abscesses developed early in the course of the disease and these were aspirated when necessary. At the conclusion of treatment positive cultures could not be obtained from any of the sites, and 20 months later, he is still clinically well.

CASE 2.—A 19-year-old Negro youth, employed as a part-time barber. This patient was admitted to the hospital on May 12, 1950 complaining of a chronic ulcer on the right thigh. About six weeks prior to hospitalization, he had noticed nodules in the skin of the right thigh, on the calves of both legs, and on the left side of the face. The nodules broke down and failed to heal. A dry cough was also present. A tentative diagnosis of virus pneumonitis or atypical pneumonia was entertained after an x-ray of the chest. However, biopsy specimens and tissue cultures from the ulcerated areas were secured and showed B. dermatitidis. The patient was desensitized with autogenous vaccine and given a course of potassium iodide for about one and one-half months without any significant improvement, although the disease appeared to be stationary. He was discharged from the hospital toward the end of June but returned the following January (1951) complaining of a large ulcerating lesion covering most of the surface of the lower right thigh and knee. During his hospital stay he received 11 deep x-ray treatments to the lesion about the right knee and considerable improvement occurred. Later he developed a small ulcerating lesion on the right elbow, one on the right hand, and other smaller lesions on the skin around both ankles. These, too, were treated by deep x-ray therapy, with resultant improvement. In October, 1951, the patient appeared to be in fairly good physical condition, but there was considerable deformity of the right knee and limitation of movement of this joint.

The patient was readmitted on Jan. 21, 1952, with many active lesions of blastomycosis on the left ankle. An x-ray of the right knee revealed fairly extensive osteoporotic changes. Stilbamidine was started at a dose of 50 mg. intravenously on Jan. 27, and on Jan. 29, 1952 the dose was increased to 150 mg. Each day thereafter 150 mg. were administered, for a total of 32 injections. In all, the patient received 5.95 gm. of stilbamidine. The patient's lesions began to clear up and healing continued even after treatment was suspended. He was discharged from the hospital on Feb. 28, 1952, and since then has had no active lesions.

COMMENT

In Case 1, inoculation occurred apparently as a result of trauma while the patient was engaged in his occupation as a rose grower in a hothouse where manure was used as fertilizer. Widespread hematogenous dissemination appearently occurred from the initial cutaneous lesion, although pulmonary involvement was not demonstrated.

Case 2 was, in all likelihood, primary in the pulmonary system and dissemination proceeded from this site.

Neuropathy involving the trigeminal nerve, which occurs frequently as a result of stilbamidine administration, occurred in both of these cases. In neither of the cases was it severe, although there were some sensory changes involving the central portion of the face. At the time this paper was written, more than two years after treatment of both cases, the neuropathy still persists, but to a lesser degree.

SUMMARY

Two patients critically ill with systemic blastomycosis have been treated successfully with stilbamidine in total doses of 5.85 gm. and 5.95 gm., respectively. One patient was extremely ill when treatment with stilbamidine was initiated, and it is considered that the drug undoubtedly was life-saving.

One patient apparently had primary pulmonary involvement with secondary cutaneous lesions, whereas in the other patient the disease apparently spread from a primary cutaneous inoculation.

Both patients are clinically and bacteriologically well at the present time, more than two years after treatment.

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TREATMENT OF CHROMOBLASTOMYCOSIS WITH CALCIFEROL

Report of Three Cases

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SAN JOSÉ, COSTA RICA

This report deals with the results of the treatment of chromoblastomycosis with large doses of calciferol. The use of calciferol in the treatment of this disorder originated with Latapí,* who believes that calciferol dissolves the granulomatous infiltrate of tuberculous diseases and thus enables the body to destroy the organism.

Since the histologic changes in chromoblastomycosis are also granulomatous in character, it occurred to me to use calciferol in patients showing the extensive nodules and patches with a hard, verrucous surface typical of the advanced stages of the disease. Previous treatment had failed to benefit these patients.

The high incidence of chromoblastomycosis in Costa Rica presents a serious problem.

REPORT OF CASES

CASE 1.—A 62-year-old man, a carpenter, was seen in the outpatient department of the hospital on Jan. 7, 1953, with the history of having injured his hand on a piece of wood while at work a year previously. A sore then appeared at the site of injury which had grown to its present size in spite of various kinds of treatment. On examination, the lesion on the back of the right hand measured 5 by 5 cm. with a fissured, verrucous center covered with small abscesses giving out a foul odor. The violet-colored margin was raised and sharply delineated (Fig. 1).

Material taken from the lesion yielded fungi regarded as causative agents of chromoblastomycosis (Dr. Alfonso Trejos).

Treatment was begun on Jan. 13, 1953, with a weekly dose by mouth of Sterogyl 15,† a preparation containing 600,000 units of calciferol. Activation of the lesions as shown by the occurrence of frequent hemorrhages was observed during the first few weeks, after which the lesion slowly flattened out. By April, only one wart-like excrescence remained. The patient went home at that time, to return in August with numerous fungi in the lesion on the back of his hand, the lesions having become active. Treatment with calciferol was started, and three months later the lesion had healed and did not yield fungi (Fig. 2).

CASE 2.—V. M. O., a 28-year-old farmer, stated that his skin trouble began eight years previously as a pimple which at first had disappeared in response to various types of treatment. The sore had slowly grown to its present dimensions.

From the Dermatological Service, San Juan de Dios Hospital (Dr. Julio C. Ovares, Chairman).

* Latapí, F.: Personal communication to the author.

† Sterogyl 15 was supplied by the Laboratories Group Roussel, Paris, France.

On examination on March 8, 1953, the greater part of the left leg from the knee down to the ankle was covered with numerous, irregularly shaped, verrucous patches, the greater number of which were confluent. The margins were sharply defined.

The mycologic findings confirmed the diagnosis of chromoblastomycosis.

Treatment was begun on the same day with Sterogyl 15 in the same manner as in the first case. The patient exhibited a similar initial exacerbation of the disorder characterized by a profuse, foul-smelling discharge from the spongiform elements, which bled profusely on the slightest contact. After this initial period, the crusts began to fall off, leaving the underlying skin hard and shiny. This patient also left the hospital before he was cured, returning late in December for more treatment. This resulted in marked improvement in the appearance of the skin. Complete healing has taken place at the time of this report.

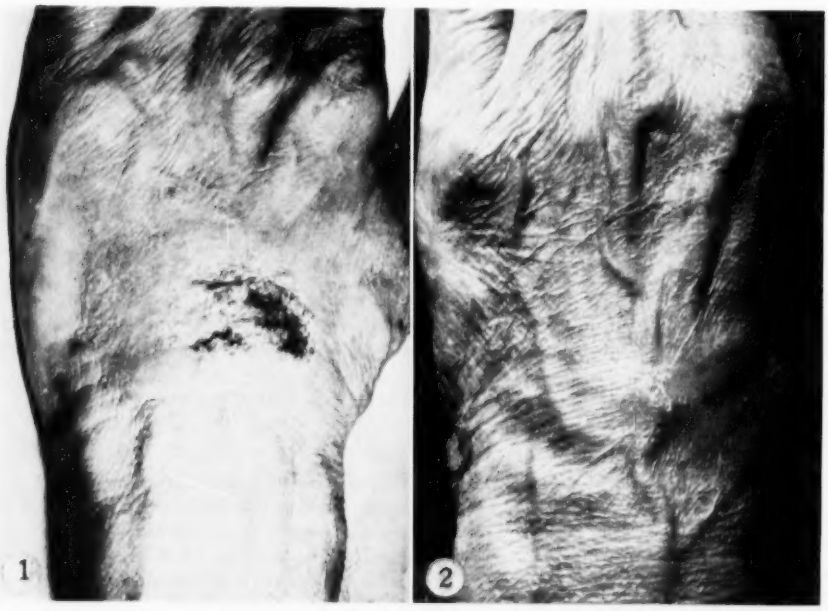

Fig. 1.—Appearance of lesion before treatment with calciferol.
Fig. 2.—Appearance of lesion after treatment with calciferol.

Case 3.—R. S. Z., a farmer, 42 years of age, stated that his skin condition began 20 years ago with a wart on the right foot. This grew during the years to its present size, involving the entire foot, lower leg, and thigh, to the extent that the patient was unable to flex the leg on the thigh. Various treatments were without benefit.

The diagnosis of chromoblastomycosis was made on the characteristic odor of the disease and on the verrucous aspects of the lesions. Numerous scarred areas attested to treatments with electrofulguration. The mycologic findings confirmed the diagnosis. Treatment was begun on Aug. 10, 1953, with the concomitant administration of calciferol and potassium iodide, the latter being given in doses of 3 gm. daily. After an initial flare-up of the process, the crusts rapidly fell off and left scars in their places. The patient was able to walk two months later, something he had not done for many years.

Three patients are currently being treated with the combination of calciferol and potassium iodide. Although a report at this time would be premature, the progress shown by these patients is more rapid than in any previously observed patients treated with calciferol alone.

SUMMARY

This report deals with the results of the treatment of three patients with chromoblastomycosis with large doses of calciferol. Various types of treatment had previously failed to benefit these patients, all of whom had suffered from the disease for many years.

One of these patients was given a solution of 3 gm. of potassium iodide by mouth daily in addition to the weekly dose of calciferol. This resulted in a relatively rapid evolution of the lesions. The combination of calciferol and iodine is producing a similar rapid regression of symptoms in three additional patients currently under treatment. No toxic effects were observed.

An explanation is offered to account for the rapid response of patients with chromoblastomycosis to the combined use of calciferol and iodine.

Apartado 4094

ACQUIRED THERMAL TELANGIECTASIA

Report of a Case

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AND
W. STUART MADDIN, M.D.
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A case of telangiectasia is presented in which the history and the distribution of the lesions strongly suggest that repeated exposure to dry heat was of etiologic significance. Schwartz, Tulipan, and Peck [1] state that telangiectasia has been noted to develop on the face, neck, and

The telangiectasia stops rather abruptly at the hemline. The telangiectatic lesions decrease in number from the posterior to the anterior aspects of the legs.

hands among those exposed to excessive heat. It was usually found on cooks and blacksmiths. The telangiectasia was usually accompanied by hyperpigmentation and freckling. Cases in which nothing other than telangiectasia developed were a rare occurrence.

REPORT OF CASE

A 41-year-old woman presented a history of repeatedly standing with the back of her legs to an electric heater each winter while employed in an electrical appliance store from 1927 to 1937. When she resumed this work, two days a week from 1949 to 1953, she continued the habit of exposing the backs of her legs to heat. From 1927 to 1936 each winter she slept with the lower third of her legs resting on an electric heating pad. She had no subjective sensations of cold, or objective clinical alterations that dictated this desire for heat. She stated that she merely liked the sensation of heat. In the spring of 1951 she bought an automobile with an underseat heater. In the winter of the same year "red spots" were noted on the backs of the legs. During the winter of 1952 she noticed that many more "spots" developed. The automobile was sold in the spring of 1953, and no new lesions were observed. There was no history of sunburn or overexposure of the legs to the sun's rays, or of any radiation therapy to these parts.

Examination revealed numerous discrete pinhead-sized telangiectases on the posterior aspects of the lower thirds of both legs. The lesions were most numerous over the tendons of Achilles. The number of lesions decreased from posterior to anterior. Only an occasional telangiectatic vessel was found on the anterior aspects of the legs. The telangiectasia stopped rather abruptly at the hemline of the dress. The skin over the involved sites was dry and covered with fine scales. There was no evidence of hyperpigmentation, freckling, or mottling. There were no telangiectatic lesions elsewhere on the body.

COMMENT

The history and the distribution of the lesions suggest that the repeated exposure to the dry heat caused the dilatation and formation of new vessels. This was probably a heroic physiologic effort on the part of the skin vasculature to maintain the local temperature within normal limits. Our observations of this case suggest that external physical factors were responsible for these irreversible telangiectatic changes. It would be of interest to know if other physicians have observed similar cutaneous changes since the advent of the underseat auto heater.

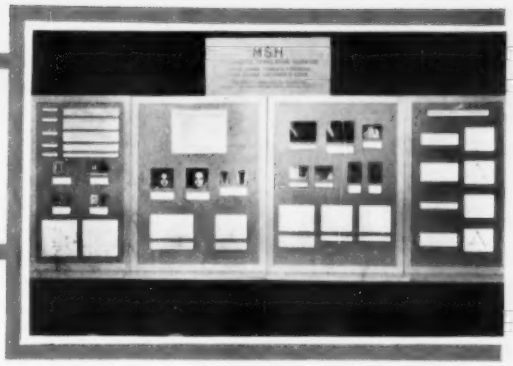
SUMMARY

A case of telangiectasia is presented in which the clinical evidence strongly suggests that chronic exposure to heat was of etiologic significance.

REFERENCE

1. Schwartz, L.; Tulipan, L., and Peck, S. M.: Occupational Diseases of the Skin, Ed. 2, Philadelphia, Lea & Febiger, 1947, p. 120.

Scientific Exhibits



MSH: THE MELANOCYTE-STIMULATING HORMONE

AARON BUNSEN LERNER, M.D.
KAZUO SHIZUME, M.D.
THOMAS B. FITZPATRICK, M.D.
AND
HOWARD S. MASON
PORTLAND, ORE.

BACKGROUND.—Melanin pigment is formed in melanocytes—cells derived embryologically from the neural crest and located in the skin, eyes, and central nervous system. Biochemical investigation has shown that tyrosinase, a copper-containing enzyme occurring in the cytoplasm of melanocytes, catalyzes the oxidation of the amino acid tyrosine to melanin, a high molecular weight polymer. The concentration of tyrosine and tyrosinase, sulfhydryl groups which can inhibit the enzyme, temperature, oxidation-reduction potential, etc., are some of the factors which play a role in melanin formation.

NEW PIGMENT FACTOR.—Injection of pituitary extracts in man produces rapid darkening of skin. A similar phenomenon was observed in animals such as frogs and fish many years ago. The active agent, a hormone elaborated by the intermediate lobe of the pituitary gland, is a small polypeptide which regulates the action of melanocytes. It has been designated the melanocyte-stimulating hormone or MSH. MSH has been referred to previously as intermedin or melanophore hormone. This hormone is a potent biologic agent, as little as 0.0000000001 gm. of purified hormone being required to darken frog skin in vitro. The finding of MSH in human pituitary glands, blood, and urine, and the demonstration that injections of MSH can produce rapid darkening of human skin provide a new approach to the study of melanin pigmentation and malignant melanomas.

EFFECT IN MAN.—Daily injections of 0.5 mg. of purified MSH may produce darkening of skin and nevi and bring about formation of new nevi. It is possible that darkening of skin and formation of new nevi under conditions of stress—such as following infectious diseases or surgical procedures—may result from increased output of MSH. In identical twins nevi occur in different sites, perhaps because the periods of stress during which MSH is released vary for two individuals. More nevi occur on the upper part of the body than on the lower, perhaps because the hormone, which is rapidly destroyed in tissues, is more readily available to the upper body through the circulatory system. Contamination of corticotropin (ACTH) with MSH accounts for the hyperpigmentation following prolonged corticotropin therapy.

PREPARATION OF MSH.—Purified MSH is prepared by extracting hog posterior pituitary powder with glacial acetic acid. Inactive material is precipitated with acetone, and MSH activity is then precipitated with ether. This precipitate is dissolved and shaken with oxycellulose. MSH eluted from the oxycellulose is subjected to a countercurrent distribution. The most active fractions are placed on paper electrophoresis, and highly purified MSH is isolated. More than a 100-fold increase in activity of MSH over the original pituitary powder is obtained.

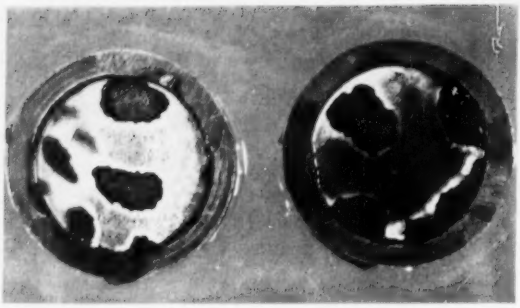
From the Departments of Dermatology and Biochemistry, University of Oregon Medical School.

This study was carried out in conjunction with the Armour Laboratories and received support from the American Cancer Society and the Damon Runyon Cancer Fund.

Shown as a scientific exhibit of the Section on Dermatology and Syphilology at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 21-25, 1954.

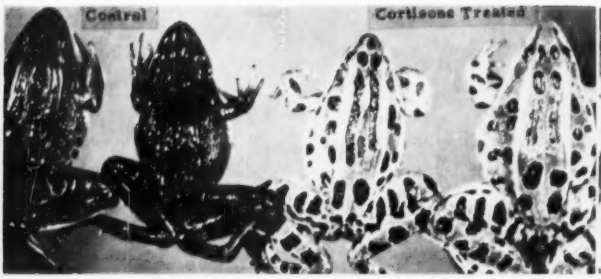
Before Hypophysectomy

After Hypophysectomy

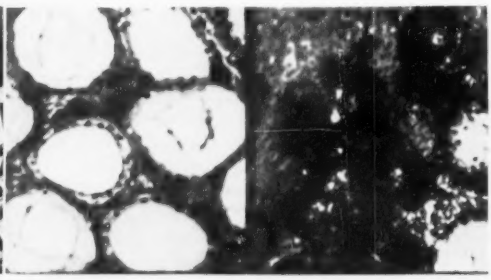


Isolated frog skin placed in Ringer's solution before and 30 minutes after addition of MSH.

The degree of darkening measured with a reflection meter forms the basis of a quantitative bio-assay for MSH in blood, urine, and tissue extracts.

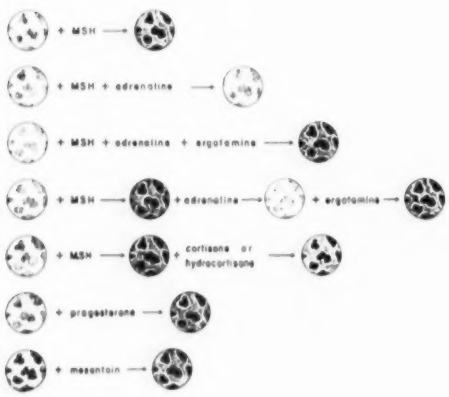


Control frogs on the left were kept in a dark room for 24 hours. The frogs on the right were treated the same except that they were given 10 mg. of cortisone before being placed in the dark. Note the prevention in skin darkening by cortisone. Hydrocortisone produced the same effect.

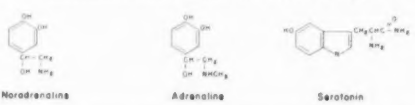


Microscopic appearance of frog skin before and 30 minutes after addition of MSH. The changes are reversible. A dispersion of melanin granules within the melanocyte occurs. There is no evidence that the cells expand or contract.

SCHEMATIC PRESENTATION OF THE *IN VITRO* EFFECT OF HORMONES AND OTHER CHEMICALS ON FROG SKIN

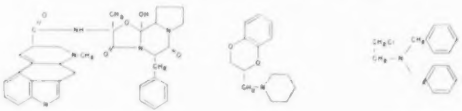


SUBSTANCES WHICH INHIBIT THE ACTION OF MSH



Noradrenaline Adrenaline Serotonin

SUBSTANCES WHICH PREVENT THE INHIBITION OF MSH BY NORADRENALINE, ADRENALINE OR SEROTONIN



Ergotamine Benzodioxane Dibenamine

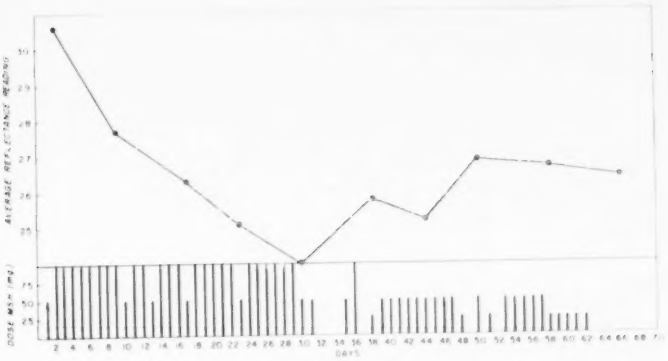
SUBSTANCES OTHER THAN MSH WHICH DARKEN FROG SKIN *IN VITRO*

Progesterone Mesantoin

Because of carcinoma of the breast this patient underwent a bilateral adrenalectomy in 1953. Addison-like hyperpigmentation was prevented by giving 50 mg. of cortisone daily.

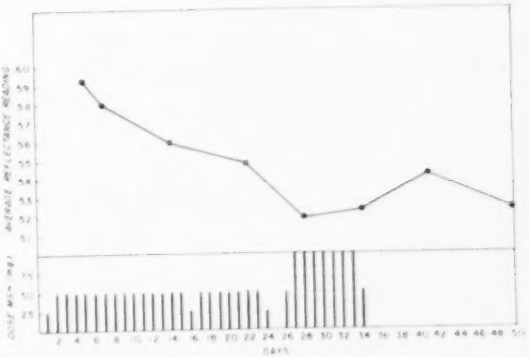
Marked hyperpigmentation occurred after injection of MSH. Total dose was 45×10^8 units. Note darkening of nevi and the appearance of a new nevus in the middle of the forehead.

The arms before and after prolonged MSH administration. The initial photograph taken one week after daily injections of MSH shows early darkening of nevi and formation of new nevi. The second photograph after 45 days of therapy shows marked darkening of nevi and appearance of new nevi.

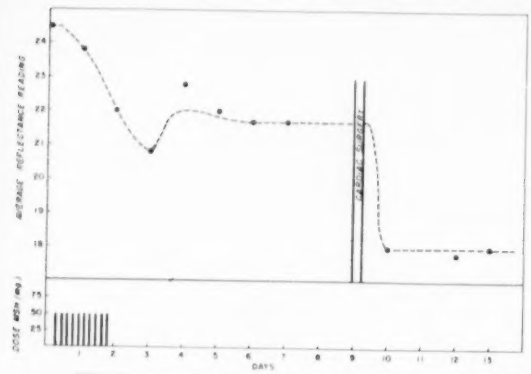


Average reflectance readings from three sites with three different filters on a subject receiving MSH for 62 days. Darkening continued until the 30th day, at which time the dose of MSH was decreased approximately one-half. The skin gradually lightened in color.

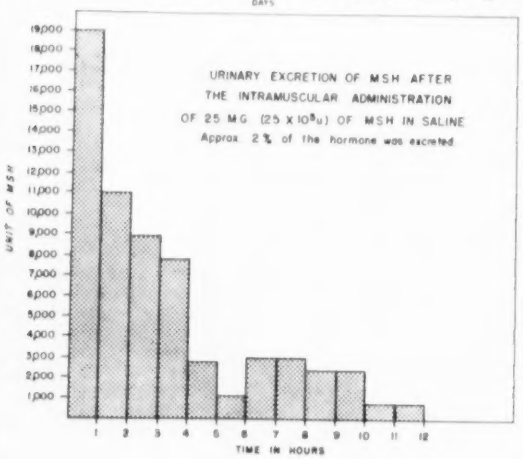
Average reflectance readings from three sites with three different filters on a subject receiving MSH for 34 days. Note gradual darkening as evidenced by decreased skin reflectance. Maximal darkening was observed after the 28th day. The skin gradually lightened in color following discontinuation of MSH.

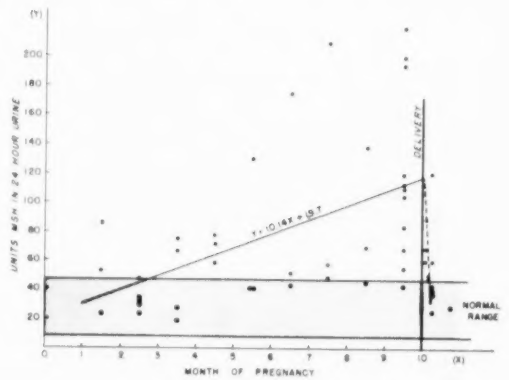


(Upper left) A patient with vitiligo before administration of MSH. (Upper center) Pigmentation increased markedly in nonvitiliginous areas after daily injection of MSH. Total dose was 4.5×10^8 units. The areas of vitiligo showed little change. Pigmentation returned to normal one month after discontinuation of MSH. (Upper right) Four months after cessation of MSH the fingernails exhibited a band of hyperpigmentation corresponding to nail growth during the period of MSH administration. (Lower left) Normal man prior to receiving MSH.; same patient, showing hyperpigmentation after daily injection of MSH totaling 3.2×10^8 units. (Lower right) Patient with vitiligo before MSH; same patient after treatment with MSH. After treatment with MSH hyperpigmentation became marked in normal areas. There was little change in the vitiligo.



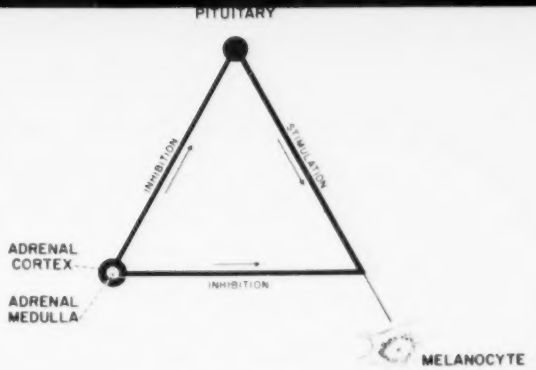
(Upper left) Average reflectance readings from two sites with three different filters on a subject receiving large amounts of MSH every four hours for 10 doses. There was a rapid increase in color as evidenced by decreased reflectance. After the third day the skin became lighter in color. However, on the ninth day the patient underwent cardiac surgery, and his skin showed marked darkening. It would seem that MSH can darken skin in a matter of hours, and that a stress reaction can produce a similar effect—presumably through increased MSH production by the pituitary gland. (Lower left) Urinary excretion of MSH after intramuscular injection of 25 mg. MSH (925×10^5 units) in saline. Approximately 2% of the hormone was excreted. (Lower right) Twenty-four hour excretion of MSH in the urine during pregnancy. Note that MSH increases throughout pregnancy but returns to normal within five days after delivery.


URINARY EXCRETION OF MSH AFTER
THE INTRAMUSCULAR ADMINISTRATION
OF 25 MG. (25 X 10⁵u) OF MSH IN SALINE
Approx. 2 % of the hormone was excreted
UNIT OF MSH
TIME IN HOURS



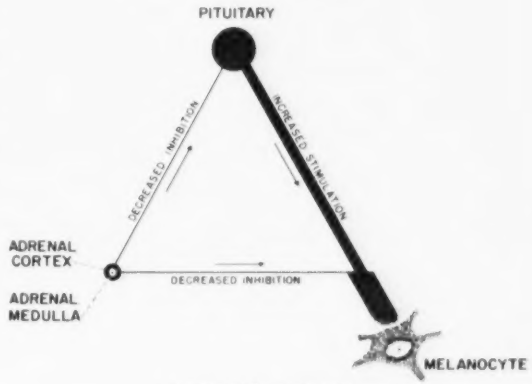
ENDOCRINE CONTROL OF PIGMENTATION

Normally, pigmentation is controlled by several hormonal factors. The pituitary gland releases MSH, which produces increased pigmentation. Hydrocortisone from the adrenal cortex inhibits the release of MSH. The greater the production of hydrocortisone, the less the release of MSH. Epinephrine (Adrenaline) and arterenol (Noradrenaline), formed by the medulla and adrenergic nerve endings, can reduce or prevent the action of MSH on the melanocyte. Other steroids, such as progesterone, and substances from the thyroid gland may play contributing roles.



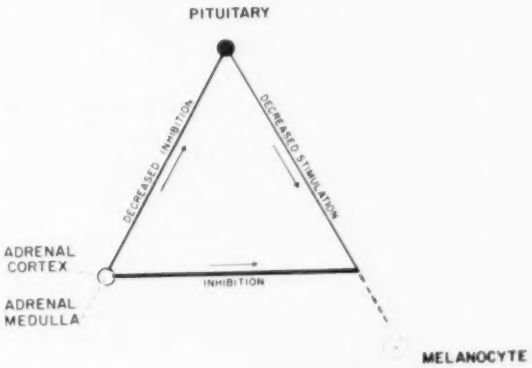
NORMAL PIGMENTATION

Decreased adrenocortical function results in decreased production of hydrocortisone. The diminution of this steroid provokes a compensatory increase in pituitary activity, so that MSH and ACTH are released in greater quantities. The melanocytes become dark because of the action of MSH as well as of factors which increase new melanin formation. If the adrenal medulla also is destroyed, a normal inhibitor of MSH—epinephrine—is removed. Thus not only is the production of MSH increased, but its function is no longer inhibited peripherally. Once the tendency to increased pigmentation develops, more pigment forms on the exposed areas, where sunlight increases the rate of the enzymic oxidation of tyrosine to melanin, and in the warm areas, such as the body folds, mucous membranes, and sites of mechanical friction. Within certain limits, the rate of the enzymic oxidation of tyrosine to melanin increases with increasing temperature. In recent wounds and sites of trauma, the increased blood supply also may provide an increase in temperature.



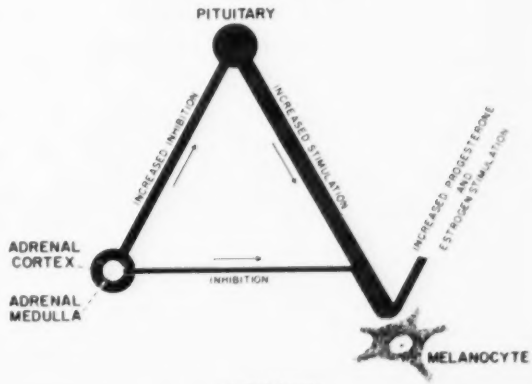
ADDISONS DISEASE

In panhypopituitarism there is decreased function of the pituitary gland and the adrenal cortex. Because of decreased pituitary activity, MSH is diminished and hypopigmentation results. The adrenal factors may be relatively unimportant.



PANHYPOPITUITARISM

In the last trimester of pregnancy hyperpigmentation occurs similar to that seen in Addison's disease. In addition the nipples, genitalia, and linea alba become deeply pigmented. More MSH is produced by the pituitary in spite of a high hydrocortisone level. Urinary excretion of epinephrine and arterenol does not change. Progesterone, which darkens frog melanocytes, is elevated during pregnancy. Whether or not progesterone augments the action of MSH in human beings is not known. Also, it is likely that some of the estrogenic substances produced during pregnancy may affect pigmentation in human beings, even though they do not act upon the frog melanocytes.



PREGNANCY

The melanocyte-stimulating hormone (MSH) is produced by the pituitary gland. In human beings MSH darkens skin, darkens pigmented nevi, and produces new pigmented nevi. MSH is largely responsible for the hyperpigmentation of Addison's disease and pregnancy. MSH may play a role in malignant melanomas, vitiligo, retiniits pigmentosa, epinephrine and arterenol metabolism, dark adaptation and night vision, and daily variation in skin pigmentation with stress.

Illustrations and Assembly:

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University of Oregon Medical School

Society Transactions

ATLANTIC DERMATOLOGICAL CONFERENCE

Bertram Shaffer, M.D., *Chairman*

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March 20, 1954

Urticaria Pigmentosa? Incontinentia Pigmenti? Presented by DR. HENRY B. DECKER, Camden, N. J. and DR. HERBERT A. LUSCOMBE, Philadelphia.

DISCUSSION

DR. PERRY M. SACHS, New York: Aspoe-Hansen described a series of cases under the long name of bullous keratogenous and pigmentary dermatitis with blood eosinophilia in newborn girls in the ARCHIVES recently. As in this case, also that of a girl, there were bullous lesions and bouts of fever and diarrhea. The feature of eosinophilia has not been noted in this patient. It is possible that the condition described by Aspoe-Hansen is a type of incontinentia pigmenti or perhaps the same condition.

DR. FREDERICK KALZ, Montreal: It seems to me that the urticarial lesions were due to penicillin. I would like to ask whether any abnormalities other than cutaneous were found? Incontinentia pigmenti was first reported as a cutaneous disorder only; as more cases were reported, other abnormalities were observed (teeth, eyes, and bones). I have seen a case with lesions only in the skin. The last issue of *Dermatologica* reports on these features and splits the disorder into two different entities.

Urticaria Pigmentosa Treated with Desoxycorticosterone. Presented by DR. FREDERICK URBACH, Buffalo; DR. COLEMAN JACOBSON, and DR. WARREN BELL, Philadelphia.

A. L., a white woman aged 54, presented brownish-purple macules and slightly elevated papules studding most of the cutaneous surface with the exception of the palms and soles. All lesions whealed on stroking and, typically, some of the lesions near the irritated ones whealed along with those directly traumatized. The wheal persisted for about 30 to 40 minutes, then gradually subsided. Duration eight years.

This patient is one of seven treated with desoxycorticosterone (DOCA), on the basis that desoxycorticosterone causes the disappearance of mast cells from animal tissues, dog mast cell tumors, and also has been reported to cause reduction of serum heparin level in a case of human hyperheparinemia. The patient was given 4 mg. of desoxycorticosterone in the form of sublingual tablets daily for a period of six months. During that period the cutaneous lesions showed a striking change. The first beneficial effect noted was that the whealing disappeared in a shorter time, then the papules began to flatten out, and finally, after about four months of therapy, the lesions began to disappear. At the present time some residual pigmentation and a few whealing lesions remain. The patient is about 80% improved. Concomitantly with the clinical improvement, certain hematologic tests having to do with heparin level in the blood, changed, as will be discussed below. The patient suffered no ill effects from the therapy, even though she was mildly hypertensive at the start of treatment. No persistent rise in blood pressure or water retention was noted throughout the course of therapy.

This patient's clotting mechanism was studied during the course of therapy with desoxycorticosterone both before and after stimulation of the lesions. The tests employed were platelet count, oil clot retraction time, prothrombin consumption, one-stage prothrombin, and heparin

titer. All of these tests, with the exception of the heparin titer, were normal. The heparin titers, expressed in gamma of protamine, behaved as follows (normal limits, 80 to 140 γ of protamine per cubic centimeter):

Before Treatment	1 Mo. After Treatment	2 Mo. After Treatment	5 Mo. After Treatment
Prestimulation			
108	120	120	80
30 min. after stimulation			
180	200	200	140
120 min. after stimulation			
160	...	...	..

The result in this patient, as in five of seven others examined, shows a significant increase in blood heparin level. The clinical improvement, together with a fall in the heparin level due to activation of the lesions in this patient, agrees well with animal studies showing a marked effect of desoxycorticosterone on mast cells. The mechanism of the action of this steroid is not known.

Dr. Frederick Urbach, Buffalo: The original reason for using desoxycorticosterone for the treatment of urticaria pigmentosa was a result of experiments carried out by Dr. Stuart of the Department of Anatomy of the University of Pennsylvania. He demonstrated that desoxycorticosterone and cortisone caused rapid disappearance of mast-cell tumors in dogs. While the action of desoxycorticosterone was more gradual, cortisone caused rapid dissolution of mast cells and massive release of heparin into the circulation, which resulted in acute bleeding phenomena in the experimental animals.

We have used cortisone in only one patient, a 4-year-old boy. A single dose of 75 mg. of cortisone caused the clotting time to rise from 3 to 21 minutes in two hours. Twelve hours later, the clotting time had returned to normal. No such rapid hematologic change occurs with desoxycorticosterone.

It must be remembered that this type of therapy is a long-term procedure. Lesions wheal less in about two to three months and flatten out in four to six months, and the residual pigmentation disappears very slowly. The patient shown today apparently has had some degree of relapse in the three months' period since discontinuence of the medication. In spite of the fact that therapy is effective only after prolonged administration of desoxycorticosterone, we feel that our results are not due to the well-known spontaneous remissions which this disease is known for, since all patients treated had been observed for from one to three years prior to any therapy, without any evidence of the slightest spontaneous improvement.

Dr. David Bloom, New York: It frequently takes many months to evaluate a drug. In this case of urticaria pigmentosa, I am not convinced that the drug had anything to do with the change in the eruption, for observation of cases of urticaria pigmentosa over a period of months frequently shows spontaneous change from a severe type to a mild type.

Coup de Sabre—Linear Scleroderma Treated with Chloroquine. Presented by Dr. John P. Scully, Reading, Pa.

The child, aged 3 years, was presented at the meeting of the Philadelphia Dermatological Society on Oct. 16, 1953. She was started on chloroquine tablets, 250 mg. each, on Oct. 23, 1953, at first one-half tablet four times a day, for one week, then half a tablet daily. This dose has recently been increased again to one-half tablet twice a day. It is the opinion of the presenter that the skin has assumed a more normal appearance, losing much of its whitish, ivory appearance, and that the skin seems to be more freely movable and less adherent to the underlying bony defects.

DISCUSSION

Dr. John P. Scully, Reading, Pa.: It was Dr. M. H. Samitz who first called my attention to the possibilities of the use of chloroquine in morphea and lichen sclerosus, and I have used it in a few cases of lichen sclerosus with amazing results so far as relief of itching of the vulva was concerned, and since this is perhaps analogous, we thought we would give it a trial.

Dr. Donald M. Pillsbury, Philadelphia: We know that chloroquine has an effect in discoid lupus erythematosus. It is not a cure-all, but in an occasional case of the disseminate type it has seemed helpful. We have therefore been using it in various collagen diseases or diseases

that seem to be related thereto. I have been following a girl with extensive scleroderma of the leg, and we believe that chloroquine has had some effect. It was discontinued for a month and the lesions seemed to become worse. That is the reason for having employed it.

Scleroderma (Acrosclerosis). Presented by DR. CARROLL F. BURGOON JR., Philadelphia.

M. W., a white girl aged 11, a normally active child with peaking of face and slimness of fingers and arms, showed a generally dry skin with Raynaud-like syndrome demonstrable in the hands. The skin of the fingers had an atrophic appearance and there was limited flexion and extension of the fingers and wrists. The skin of the arms and trunk had a lardaceous feel. The vascular markings on the thighs were prominent, and the skin was not normally pliable. The left knee flexion was impaired. Finger flexion of metacarpophalangeal joints and right knee flexion and extension were normal.

The parents stated that they first observed a slimness of the fingers and hands which had been present for two to three years. This was attributed to inability to gain weight and general asthenic build. One year ago they observed inability to flex the fingers completely. In the past three years the parents have noted peaking of the face and thinness of the arms, also prominence of blood vessels on the thighs. There has been no significant progression in the past year. There are two siblings, one being a heterologous twin of the patient. A paternal uncle has diabetes mellitus.

Results of Goniometry

	Sept. 30, 1953 Deg.	Nov. 23, 1953 Deg.	Feb. 5, 1954 Deg.
Right Hand			
Active extension	15	42	44
Active flexion	35	35	45
Finger flexion	85	75	65
Left Knee			
Flexion	72	115	112
Extension	180	180	180

A complete blood count on Sept. 29, 1953, revealed 12.4 gm. hemoglobin per 100 cc., 5,150,000 erythrocytes, 5,000 leucocytes, 44% polymorphonuclear leucocytes, 44% lymphocytes, 6% monocytes, 4% eosinophiles, 2% basophiles. The sedimentation rate on Oct. 2, 1953, was 5 mm. in 60 minutes (corrected). A urinalysis on Sept. 28, 1953, was within normal limits. A roentgenogram of the chest showed nothing abnormal. Swallowing function was normal with normal-appearing esophagus. Roentgenograms of the hands and wrists showed nothing abnormal in the bones or soft tissues of either hand.

The report on the biopsy specimen from the arm was: "Thin but not atrophic epiderm, thickened corium and normal fat. Collagen was homogeneous and had but few nuclei. There were no outstanding vessel changes. (Dr. Herman Beerman). Diagnosis: Compatible with scleroderma."

The patient has been treated with potassium paraaminobenzoic acid, 6 to 7 gm. a day, for four months, and with physiotherapy.

DISCUSSION

DR. GEORGE C. ANDREWS, New York: This patient has a history of an accident at the age of 3 years, with a fractured skull, and I think it would be a good case on which to do an encephalogram. Drs. Taylor and Pacella (*J. Nerv. & Ment. Dis.* **109**:42-47 [Jan.] 1949) have demonstrated that in most cases of scleroderma there are encephalographic changes.

DR. BERNARD APPEL, Boston: At the Boston City Hospital a number of cases of scleroderma which on casual examination showed no other apparent systemic changes, were studied more thoroughly, particularly with pulmonary function studies by the Department of Inhalation Therapy, and were discovered to have definite beginning disturbance of ventilation and pulmonary

function. I, therefore, would like to suggest that every case of scleroderma which is seen by the dermatologist be referred for more thorough and complete physiological study of the pulmonary functions.

DR. DONALD M. PILLSBURY, Philadelphia: We had hoped to present a patient from this hospital with a very similar condition—in fact, almost a twin with regard to presenting symptoms. The other patient, whose age is 10 years, I believe, had received cortisone in doses of 100 to 150 mg. daily for three years with no effect on the diffuse sclerodermatous changes. This type of case is rather new in my experience. I should like to hear from anyone who has had an opportunity to follow such a patient through to adult life. We are afraid that the outlook is bad, and if there is some good news for the mother of the patient, it would be appreciated.

DR. ORLANDO CANIZARES, New York: I should like to know if anybody has ever seen a case of localized scleroderma (morphea) later developing into the generalized type of scleroderma. I think it should be made clear that there are two types. There is a tendency today to consider scleroderma one disease.

DR. CHRIS J. ZARAFONETIS, Philadelphia (by invitation): A woman who had a morphea patch for 15 years on the back, later developed systemic sclerosis or scleroderma.

DR. BERTRAM SHAFFER, Philadelphia: I have seen cases of scleroderma in which the history gave a form of localized scleroderma eventually becoming generalized.

Lipoid Proteinosis. Presented by DR. FREDERICK URBACH and DR. MARGARET GRAY, Philadelphia (both by invitation).

F. J. P., a white man aged 26, has been hoarse as long as he can remember. He has had canites of the right eyebrow and temple since infancy. There is no history of dyspnea, dysphagia, or swelling of the tongue. Verrucous lesions have been present on the eyelids since birth, on the elbows since 1949, and in the axillae since 1951. Mucosal involvement was not previously noted by the patient. He stated, when the lesions were pointed out to him, that his mouth has always looked like that. He had the usual childhood diseases and almost died of whooping cough. He has had frequent sore throats and had a tonsillectomy in 1932. His father is living, with gallbladder disease. His mother is living, but is diabetic; she has had two miscarriages. His sister is living and well. One grandmother, now dead, was also diabetic.

Physical examination reveals a well-developed and well-nourished white man in no distress. His voice is very hoarse. Complexion is light. The lower lip protrudes. The heart and lungs were normal, blood pressure 122/76. Abdomen normal. The skin was generally dry. There was canities of the middle third of the right eyebrow, and the right temple. Along the borders of both eyelids were waxy excrescences appearing like a string of beaded pearls. The conjunctivae were normal. There was mild acneiform pitting of the face. In the dome of both axillary folds were linearly arranged, confluent, pearly nodules, slightly brownish in hue. Over the olecranon process and extending along the upper third of the ulna were confluent patches of hyperkeratotic warty papules. The entire lower lip was thickened and firm, and infiltrated with a whitish-gray patchy material. The tongue was definitely thickened and whitish, the papillae less marked than normal, and the anterior part crossed by deep linear transverse grooves. The fauces and buccal mucosae showed patches of whitish-yellow, plaque-like infiltrate. The soft palate was studded with yellowish-gray nodules. The frenulum of the tongue was markedly thickened and showed bands of whitish infiltrate replacing the raphae.

The cholesterol total was 183 mg. per 100 cc., esters 136 mg. per 100 cc. The total lipid content was normal. The fasting blood sugar was 76 mg. per 100 cc., the blood urea nitrogen normal. The complete blood count was within normal limits.

The report on the biopsy specimen was lipoid proteinosis.

DISCUSSION

DR. DAVID BLOOM, New York: This is a very rare type of lipoidosis, and I am grateful for the opportunity to see this case. The first case I have seen was that reported by Wise and Rein (ARCH. DERMAT. & SYPH. **37**:201 [Feb.] 1938). These cases are of recessive inheritance; the parents are free of the eruption and one-fourth of the siblings are affected.

DR. MAURICE J. COSTELLO, New York: I presented a case of this disease involving the lips, the floor of the mouth, the buccal mucosa, and the larynx about three times in the last year at the New York societies. This patient recently improved on the administration of cortisone.

Sarcoidosis, with Bone Involvement of the Digits, Treated with Chloroquine. Presented by DR. M. H. SAMITZ and DR. JACK WEINER, Philadelphia, and (by invitation) DR. H. BOGAERT, Philadelphia.

E. M., a Negro woman aged 23, presented a discrete, hyperpigmented, pinhead to split-pea-sized, papular eruption involving the cubital spaces, the anterior axillary folds, the neck, face, and ears. It was most intense in the cubital spaces; on the neck there was a suggestion of a moniliform arrangement, while on the face and ears the papules were sparse and scattered. On the alae nasi were split-pea-sized, violaceous, firm papules. Located on the radial aspect of the left wrist was a patch of confluent papules forming a hyperpigmented plaque. The fourth digit of the left hand and the second, third, fourth, and fifth digits of the right hand showed fusiform swellings, which were firm and somewhat tender on palpation.

The patient was treated with chloroquine, 100 mg. three times a day, with prompt relief of her pruritis. The digital swellings became softer, almost putty-like, on palpation after only two weeks on therapy. She has continued on the same dosage to date, with slight involution of her eruption.

Sarcoid. Presented by DR. JOHN F. WILSON and DR. JOSEPH K. CORSON, Philadelphia.

M. L., Negro woman, aged 60, had small firm subcutaneous nodules about the nose. The patient was given chloroquine, 250 mg. twice a day from July, 1953, to time of presentation, with slow improvement. The patient claims great improvement following the BCG vaccination.

Sarcoid. Presented by DR. HERMAN BEERMAN, Philadelphia, and (by invitation) DR. JOHN H. YEAMAN, Salisbury, Md.

The patient was treated in July 1953, with quinacrine (Atabrine), 0.1 gm. three times a day; on Sept. 27, 1953, chloroquine, 250 mg. three times a day; with procaine penicillin, 6,000,000 units, November, 1953.

Sarcoidosis. Presented by DR. CARROLL S. WRIGHT and DR. MEYER L. NIEDELMAN, Philadelphia.

A. T., Negro woman aged 34, has scattered grouped nodules in and below skin. The patient has been treated with corticotropin (ACTH), cortisone, urethan, and bismuth sodium triglycollamate (Bistrimate) tablets, without effect. A six months' trial with quinacrine and chloroquine (Aralen) was ineffective. She has been on isoniazid (isonicotinic acid hydrazide; Nydrazid), 200 mg. daily, for three months without any benefit.

Sarcoidosis, Cutaneous and Pulmonary, Presented for Therapeutic Suggestions. Presented by DR. CARROLL F. BURGOON JR. and DR. DOROTHY R. LYNN, Philadelphia.

C. H., a Negro woman aged 37, presented a large, tumor-like lesion with overlying depigmentation and a slight amount of erythema on the right malar eminence extending to the right side of the nose. There were similar plaques on the proximal lateral aspect of the arms and on the buttocks.

The patient has been treated with arsenic trioxide, with no effect, isonicotinic acid hydrazide, 300 to 400 mg. a day, with no effect. The present therapy is 300 mg. of quinacrine a day.

DISCUSSION

DR. MAURICE J. COSTELLO, New York: Every one of these cases brings out the fact that we see muscle involved in the lesions of sarcoid more frequently than was supposed in the past. Recently at Bellevue, in studying a case, a muscle biopsy was done, and the lesions of sarcoid were seen profusely throughout the muscle; and it is a common experience among surgeons to remove a node in the neck and accidently remove a portion of the scalenus muscle and also

find sarcoid there. Another test we have used it to inject equal parts of cortisone solution and tuberculin into tuberculin-negative cases, neither producing a reaction alone, but the combination producing a 1 + reaction.

DR. MEYER L. NIEDELMAN, Philadelphia: It is interesting to note that patient A. T., the Negro woman aged 34, also had subcutaneous nodules of Darier-Roussy type which have disappeared leaving depigmented areas. Although her scalp lesions have improved, her bone defects are worse. From the medical department of the Falu Hospital comes a report by Dr. S. E. Fagerberg, whose study covers the period 1944 to 1951 and deals with 58 patients observed among a total of 18,432 admitted to that hospital. After the omission of 4 patients, there remained 54 (25 men and 29 women) about whose subsequent fate information was available. The ages of these patients ranged from 20 to 69 years. In addition to the 7 patients who had died, 10 were found on reexamination to be subjectively and objectively well and 9 felt well but still showed signs of the disease, such as changes in the lungs, eyes, or bones. The others still presented various subjective and objective manifestations of the disease. In 5 patients, involvement of the lungs or eyes entailed severe invalidism, and in 32 there was impairment of health but not severe invalidism. In view of the comparatively short observation period and the prospect of progress of the disease in some of these patients, Dr. Fagerberg is dubious about the prognosis of a disease that has been given the somewhat misleading name of benign lymphogranulomatosis. With only 10 patients showing both subjective and objective recovery on reexamination, the adjective benign seems to be a misnomer. The prognosis seems bad when there is involvement of the lung parenchyma.

DR. DAVID BLOOM, New York: I believe that cases of so-called sarcoidosis in the Negro are not the same as those seen in Caucasians. It is a form of tuberculosis. One finds a high percentage of tuberculin reactivity in these patients, and there are frequently present, besides sarcoid lesions, definite tuberculous lesions. Many of these patients have associated visceral tuberculosis or develop tuberculosis later. Because of this I consider that treatment with steroids should be given with the greatest caution.

DR. FRANCIS A. ELLIS, Baltimore: In 1938 I found in the literature 10 cases of "Ostitis tuberculosa multiplex cystoides (Jüngling), (Ellis, F. A.: Ostitis Tuberculosa Multiplex Cystoides" (Jüngling) in Patient with True Tuberculosis of the Skin, *Internat. Clin.* **4**:154 [Dec.] 1938; and Ellis, F. A.: Jüngling's Ostitis Tuberculosa Multiplex Cystoides" Is Not Cystic Tuberculosis Osteitis, *Acta Med. scandinav.* **104**:221, 1940) associated clinically with sarcoid-like picture in which the histopathology of the skin lesions was more that of a lupus vulgaris picture. Why should we call these lesions Darier-Roussy sarcoid? We know that in the Negro the sarcoid cutaneous reaction may be different from that in the white; that is, the histopathologic picture may be that of noncaseating tuberculosis. I disagree with Dr. Bloom because, even if the cutaneous picture varies somewhat, these are still sarcoid. The evidence, I think, is far more in favor of sarcoid than of tuberculosis. We do not see many of these patients die of tuberculosis. At the Atlantic Conference we presented (Ellis, F. A., and Robinson, H. M.: Ostitis Tuberculosa Multiplex Cystoides (Jüngling) and Its Relation to Spina Ventosa, with a Preliminary Report of a Case, *Bull. School Med. Univ. Maryland* **18**:115 [April] 1934) a man with extensive bone changes of ostitis tuberculosa multiplex cystoides of Jüngling. He eventually died, but did not die of tuberculosis. He had no pulmonary lesions, and his biopsies showed more a lupus-vulgaris-like picture.

DR. FREDERICK REISS, Norwalk, Conn.: I should like to ask the presenters of Case E. M., Negro woman aged 23, whether the histopathology of that case is typical of sarcoid. I was under the impression that it could be compatible with lupus miliaris disseminatus faciei rather than sarcoid. In relation to Dr. Ellis' remarks, I believe that we should be clear that sarcoid is a histopathologic reaction and not a disease entity. During my 20 years in China I saw a number of cases of leprosy which looked exactly like sarcoid, and no histopathologist and no clinician would have been able to make a differential diagnosis without further investigation. A good many South American dermatologists and pathologists are convinced that cases af sarcoid are nothing but a form of leprosy. There are changes in the bones in tuberculoid leprosy which are exactly the same as in sarcoid, and the only distinction is that lymph node changes are rarely of a sarcoid nature. However, there are rare cases of tuberculoid leprosy in which sarcoid-like changes in the lymph nodes have been observed.

DR. LEON BABALIAN, Portland, Me.: I am very much interested in Dr. Reiss's opinion concerning a possible relationship between sarcoidosis and leprosy. It was also the opinion of Lomholt (cited by Pautrier in "Nouvelle pratique dermatologique," edited by Darier and others, Paris, Masson & Cie, 1936, Vol. 3, p. 732). Twenty years ago this author treated successfully cases of sarcoidosis with injections of a by-product of chaulmoogra. To me this factor was quite possible in the Negro woman aged 23, who presented whitish spots in addition to the lesions of sarcoidosis. In fact, I found no trace of anesthesia on these leucodermic spots and my examination failed to reveal any sign of leprosy in this case. I do feel, however, that it would be worth while to try some antileprosy treatment.

DR. FRED D. WEIDMAN, Philadelphia: As to Case M. L., a Negro woman aged 60, I believe the histology is not that of sarcoid. The epithelioid cells are distributed diffusely; they are marked fibrillar affairs; there are quite a number of giant cells, and I think it is more compatible with tuberculosis miliaris faciei. I think that is also compatible clinically. I thought the lesion on the nose had a rather redder and more tumid character than that of most sarcoids; so I would suggest that as the diagnosis in this case. With the history of additional lesions on the face previously, the word disseminatus, which is sometimes tacked on, is apropos. As regards the Negro woman A. T., aged 34, I thought the histologic picture correct for sarcoid.

DR. BERNARD APPEL, Boston: It seems to me that a very important element has been introduced into the discussion of these cases by Dr. Weidman and Dr. Reiss, namely, the resemblance histologically in some cases to both leprosy and tuberculosis. In Boston last year Dr. Jose M. Fernandez of Rosario, Argentina, spent almost a year with us doing some special research work in leprosy. He showed me slides which looked exactly like what we call sarcoidosis but which he said were leprosy, and I believe his opinion, since he is a well-known leprologist, may be taken as correct. He brought out the very significant histological similarity among these three diseases and emphasized that some European and some South American pathologists claim that it is almost impossible in some cases to differentiate between them. As to the use of corticotropin, I think it was agreed that it was of no value in sarcoidosis until the group working with Dr. Herman Beerman showed how effective it is when injected locally. However, we have had a patient with generalized sarcoidosis who had dermatological, osseous, pulmonary, and optic lesions of many years' duration with an extraordinary degree of improvement following a rather prolonged and, I will admit, a somewhat dangerously extensive use of corticotropin in repository gel. We gave her daily injections of appreciable amounts, starting with 40 units twice daily for 10 days, then gradually reduced this to 40 units once daily for 4 days, then 20 units daily, and ended with 10 units daily. During 38 days we gave her a total of 1,330 units of corticotropin intramuscularly. We also took the precaution of using penicillin procaine intramuscularly with each injection. It is now more than four months since her last treatment and the general improvement is still maintained. Therefore, there may be some cases of sarcoidosis in which the systemic administration of corticotropin may be of some value.

DR. ALFRED HOLLANDER, Springfield, Mass.: I have just come back from a visit to Peru. I think that the South American observers rarely see sarcoidosis of the Boeck type. When I was first shown cases of tuberculoid leprosy—I have just seen three new cases during the last week—it was very difficult in the beginning to make a clinical diagnosis and to decide whether they were sarcoidosis or leprosy. Careful study of patients with tuberculoid leprosy may reveal especially lesions of the face of deep red color and anesthesia of some areas of the affected skin, as well as thickened nerves. The histological picture can be differentiated because most of the cases of tuberculoid leprosy show regular tubercle formation with Langhans type giant cells, which in cases of Boeck's sarcoid are not seen. Few, if any, Mycobacteria leprae are found.

DR. PAUL GROSS, New York: Without being facetious, I should like to say that one cannot make a histological diagnosis of sarcoidosis, but can only speak of sarcoid reaction or sarcoid structure. To make the diagnosis of sarcoidosis, a complete clinical and laboratory study is necessary. When the criteria of sarcoidosis are fulfilled by such an examination, leprosy and other forms of granulomas can be ruled out. With reference to Case C. H., the Negro woman aged 37, the skin lesion in this patient is really a circumscribed lupus pernio. It is of historic interest that it was in a case of lupus pernio that Kreibich first described in 1904 the presence of bone lesions which are now known as ostitis tuberculosa multiplex cystoides.

DR. HERMAN BEERMAN, Philadelphia: Dr. Gross has stated essentially what I wished to say. I do not believe that the diagnosis of sarcoidosis should be made on a histologic basis alone. A sarcoid-like reaction may be due to many causes: sarcoidosis, leprosy, tuberculosis, beryllium, and foreign bodies. I think Dr. Weidman had a patient in whom a vegetable fiber produced such a picture. Syphilis, of course, is well known to do the same thing. One cannot take a section and differentiate these processes unless one finds a foreign particle, a bacillus, etc., by various means in the section. On the other hand, these diseases are frequently so similar that there is a tendency to go to the other extreme and say that because they look alike and have many features in common, therefore they are the same disease.

DR. JOHN F. DALY, Burlington, Vt.: I noticed that some cases were treated with chloroquine. In an article by Dr. Shaffer (Cahn, M. M.; Levy, E. J., and Shaffer, B.: The Use of Chloroquine Diphosphate [Aralen] and Quinacrine Hydrochloride [Atabrine] in the Prevention of Polymorphous Light Eruptions, *J. Invest. Dermat.* **22**:93 [Feb.] 1954), mention was made of optic side-effects from chloroquine, and having seen a few cases myself, I wondered if this would not give us an opportunity to see people who have observed the optical disturbances we occasionally see with chloroquine. Quinacrine has also been reported to cause optical disturbances.

DR. BERTRAM SHAFFER, Philadelphia: We did not see cases with ocular disturbance. We did observe a number of cutaneous reactions to chloroquine (Aralen). It was used in patients who were light-sensitive, and that may account for the side-reactions we saw.

DR. MAURICE J. COSTELLO, New York: I have seen ocular changes fairly frequently. It is not uncommon for a person, after taking chloroquine for a few weeks, to complain of inability to accommodate. I had a patient who suffered an automobile accident because of the fact that he could not accommodate. It is a well-known toxic effect of chloroquine.

Discoid Lupus Erythematosus? Lichen Planopilaris? Presented by DR. HERMAN BEERMAN and (by invitation) DR. RAYMOND A. KRAIN and DR. HAROLD COLBURN, Philadelphia.

B. D., a Negro aged 77, in 1947 developed a few pruritic "lumps" on the lower extremities. He constantly scratched these and subsequently developed verrucous hypertrophic lesions on the lower extremities. At about this time he developed pruritus of the scalp and three areas of alopecia.

The scalp showed three areas of alopecia and atrophy, enlarged follicles, and depigmentation. Legs: Over each lower extremity plaques were present which were verrucous in nature. Interspersed were areas of depigmentation and atrophy. There were suggestive white infiltrative lesions on the buccal mucosa.

The complete blood count and urinalysis were within normal limits.

The report on the biopsy specimen was as follows: "8/17/50: Scalp. Lupus erythematosus (some resemblance to senile keratosis). Leg. Hyperkeratosis with benign verrucous epithelial hyperplasia."

The patient has been treated with 500 mg. of chloroquine daily for three months, with no significant result.

DISCUSSION

DR. ALBERT SHAPIRO, Baltimore: This patient is beginning to show hypertrophic verrucous lesions on the scalp, where he has typical lupus erythematosus. I believe, therefore, that the tumors on the legs are merely an evidence of the same process, a very unusual verrucous form of lupus erythematosus.

DR. FRANCIS A. ELLIS, Baltimore: I disagree. I believe this patient has hypertrophic lichen planus, in which we have the picture of lichen planus pilaris or lichen planus acuminata et atrophicans. Clinically and histologically it may look like lupus erythematosus. The histology usually can rule out lupus erythematosus. The fact that we get a well-defined infiltrate around the bases of the follicles may suggest that there is a deep infiltrate if part of the follicle does not appear in the slide to identify its perifollicular location. (Ellis, F. A., and Kirby-Smith, H.: Lichen Planus et Acuminatus Atrophicans [Feldman], ARCH. DERMAT. & SYPH. **43**:628 [April] 1941.) Graham Little has written up these cases associated with spinous lesions under the title of lichen spinulosus with pseudopelade, making the mistake because he did not associate the small spinous lesions as a form of lichen planus.

DR. PAUL GROSS, New York: I agree with Dr. Ellis that the lesions on the legs are those of hypertrophic lichen planus. Of course it is unusual to see hypertrophic lesions associated with lichen planopilaris of the scalp, but it is not unusual to find typical lichen planus plaques in combination with lichen spinulosis and pseudopelade-like lesions of lichen planopilaris.

Dermatofibroma? Dermatofibrosarcoma Protuberans? Presented by DR. HERBERT A. LUSCOMBE, Philadelphia, and DR. A. G. PRATT, Camden, N. J.

J. J., a white man aged 60, presented on the top of the right shoulder, extending to the base of the neck, a fairly well marginated, dusky red, firm, nodular patch measuring 12 by 10 cm. Near the medial edge of the patch was a large, egg-sized, firm tumor extending about 2 cm. above the surface of the patch. In the lateral aspect of the involved area there were several raised nodules, each about 1 cm. in diameter.

The patient was first seen in 1948, at which time he had a skin tag on the right shoulder. This was surrounded by an erythematous, firm area. Over the next five years the patch enlarged very slowly, with formation of small tumors in the patch. The patient has allowed these tumors to be excised from time to time, but would not submit to complete excision. In the past eight months the patch has doubled in size and one larger tumor has formed. In 1923 the patient lost his right index finger by surgical removal for infection. A kidney stone was removed in 1943. He was said to have papilledema of the right eye in 1947. About 1948 he started taking nitroglycerine for "distress in chest." He is not acutely ill, but has a sallow appearance. Medical examination revealed optic atrophy of the right eye.

Reports on the biopsy specimens were as follows:

1/13/53	Fibromatous polyp	4/ 5/51	Myxofibroma of skin
6/ 8/48	Dermal fibrosis	4/22/52	Neurofibroma
6/22/48	Soft fibroma	5/ 6/52	Neurofibroma
6/21/50	Neurofibroma	5/11/53	Neurofibroma
1/25/51	Neurofibroma		

The patient has received no treatment for the cutaneous condition.

DISCUSSION

DR. ANTHONY CIPOLLARO, New York: This is a classical example of dermatofibrosarcoma protuberans and the best proof of that is the histological reports. There have been nine pathological reports, and all of the fibrous element. This is a disease which is relatively benign even though it seems to spread peripherally and locally. There are some reports in the literature of this disease assuming a malignant character, but on the whole it is a relatively benign disease. It tends to recur if the entire area is not excised at once.

DR. GEORGE C. ANDREWS, New York: In spite of the benign histological sections and the realization that it is essentially a sclerosing process, I am not satisfied with the diagnosis of dermatofibrosarcoma protuberans in this case for the reason that the lesion, which has grown since June, is soft and elastic on palpation. The lesions of dermatofibrosarcoma protuberans are hard. I would be inclined to think rather of reticulum cell sarcoma or lymphosarcoma in this case. I think you should perform a biopsy of that soft, elastic nodule that has arisen on the shoulder more recently. In dermatofibrosarcoma protuberans it is quite common to have that conflict of opinion about differentiation from lymphoma, and I have known such mistakes to occur before. This man has never had any roentgen ray treatment. He has a progressive lesion, and it may be radiosensitive, in spite of the biopsy. I have followed a case of dermatofibrosarcoma protuberans for the past 10 years. The patient has had numerous excisions by plastic surgeons, and each time there has been local recurrence. The man is in miserable shape. It is a disabling disease and prevents him from working now. He becomes weak and exhausted from pain. I am sure that the best treatment is solid carbon dioxide. I have treated cases successfully with solid carbon dioxide without recurrence. Sometimes general anesthesia may be necessary, if the area involved is extensive.

DR. FREDERICK REISS, Norwalk, Conn.: I agree with Dr. Andrews. Dermatofibrosarcoma protuberans generally occurs on the abdominal areas. Besides what Dr. Andrews said as to the large tumor being very soft, it should be borne in mind that the consistency and shape of dermatofibrosarcoma clinically resembles that of keloids. In this instance the skin surrounding

the large tumor is smooth—atrophic-looking. I believe another biopsy should be done because the clinical characteristics are not sufficient to complete the diagnosis. I believe it is probably reticulum cell sarcoma.

DR. MAURAY J. TYE, Haverhill, Mass.: I had occasion to see a case very similar to this, with lesions that were firmer around the periphery. Several sections were cut pathologically because the entire lesion was removed, and they were shown to Dr. Shields Warren and Dr. Wilbert Sachs. They made the following diagnoses on the various sections, namely, noduli cutaneae, perineural fibroma, and sclerosing hemangioma. It is now four years since the original diagnosis and treatment. The patient has shown no evidence of sarcoma.

DR. FRED D. WEIDMAN, Philadelphia: In my one case the lesions were located on the outside of the thigh of one of our student hurdlers. In that case, as here, there was a zone of fibrous regression surrounding the active nodules. For a long time there was a patch in which there were characteristics of nodular subepidermal fibrosis clinically. The special nodules developed later. I think that the matter of softness and firmness depends very largely on the stage. After all, *sarcos* means flesh, which is soft, and sarcomas are soft, fleshy tumors, and I think that the matter of softness or hardness could be a function of the stage of the disease. I agree with Dr. Andrews that the answer will come only with examination of a piece of tissue from the center or near the center of that softer, elastic part of the lesion.

Kaposi's Sarcoma. Presented by DR. HERMAN BEERMAN, DR. RAYMOND A. KRAIN, and DR. HAROLD COLBURN, Philadelphia.

S. B., an elderly white man, presented violaceous, hemorrhagic, infiltrative papules, nodules, and plaques on both legs. Some of these lesions had a bullous appearance. There was an ulcerated lesion on the right great toe. Above the ankle these lesions had a constricting appearance. There was cardiac enlargement. Onset was in 1936 with a single papule on the right great toe. Subsequently there developed plaque-like and lymphangiomatous-appearing lesions. In 1951 the lesion on the right great toe became ulcerated.

The patient has had no operations or serious illnesses. He was admitted to the hospital in 1940 with a diagnosis of Kaposi's sarcoma. In 1952 he had partial treatment with nitrogen mustard. He did not tolerate this, and the treatment was stopped. In 1953 he was again admitted to the hospital with cellulitis of the right leg.

An electrocardiogram showed left ventricular strain. The complete blood count and urinalysis were within normal limits. Roentgenogram of the chest and gastrointestinal survey were essentially normal, as was sigmoidoscopy. Hematology consultation revealed no pertinent findings.

The report on the biopsy specimen was Kaposi's sarcoma (Dr. Fred D. Weidman, May 11, 1940).

Kaposi's Sarcoma. Presented by DR. CARMEN C. THOMAS and (by invitation) DR. DONALD MADDEN, Philadelphia.

DISCUSSION

DR. ANTHONY CIPOLLARO, New York: I should like to discuss Case C. C., the man aged 63, with atrophy of the leg. The thought came to me, without having read the history, that this was probably the result of not using that extremity or of the use of radiation with high-voltage, filtered x-ray for the treatment of this disease, which is really a rather superficial process. Perhaps the atrophy is the result of over-radiation rather than the result of the disease, Kaposi's sarcoma.

DR. FREDERICK REISS, Norwalk, Conn.: I agree with the diagnosis and suggest the use of quinacrine in an early case of Kaposi's sarcoma. A few months ago at the New York Academy of Medicine I presented such an early case, which showed a remarkable remission after treatment with quinacrine. Apparently it was not a spontaneous regression, but definitely a therapeutic response.

DR. BERNARD APPEL, Boston: Has anyone any experience with the reported cure of this disease with large doses of penicillin—a report which came out in the European literature some years ago? I have never seen any one or talked with anyone who has seen a cure of this disease with penicillin.

DR. ORLANDO CANIZARES, New York: We have treated several cases of Kaposi's sarcoma with penicillin, using the technic described by Dr. Grispan in Argentina. We obtained no beneficial results at all.

DR. ANTHONY CIPOLLARO, New York: My experience has been similar.

DR. CARROLL F. BURGOON, Philadelphia: It is my recollection that he had the atrophy before he had any irradiation, and had it for a significant number of years before he was either diagnosed or treated.

DR. FRANCESCO RONCHESE, Providence, R. I.: In Italy, it is common for a clinic to see 15 to 20 cases of Kaposi's sarcoma in a year, and it is my impression that treatment with penicillin has been successful. I treated two severe cases with penicillin with no result, after learning of favorable reports also from Argentina.

DR. CARMEN C. THOMAS, Philadelphia: This patient's mentality is not good enough to get a history of the exact date of onset, but since he has been in the hospital off and on since 1945, and radiation was not given prior to that time, and he did have the atrophy on the first admission, the atrophic changes cannot be attributed to irradiation.

Cutaneous Lymphoma. Presented by DR. CARROLL F. BURGOON JR. and (by invitation) DR. T. F. MCNAIR-SCOTT, Philadelphia.

J. S., a white boy aged 8 years, presented small, depigmented areas on the buttocks and small papules on the arms in July, 1953. Within the next two months there was a spread of the lesions to involve the legs, new lesions continually appearing on the arms, legs, and trunk. The lesions became very scaly, and one on the left elbow, after trauma, broke down and formed a large ulcer. A similar nodule which became enlarged on the right forearm slowly regressed and disappeared with residual scarring. All of the skin lesions have been completely asymptomatic, and there has been no apparent change in the general health. Since October, 1953, one new lesion has developed on the buttocks with associated right inguinal lymphadenopathy. All the skin lesions have been slowly regressing. The patient is otherwise active and normal.

The report on biopsy specimens was as follows: Malignant histiocytomas (Dr. Fred D. Weidman). Mycosis fungoides (Dr. Herman Beerman). Lymphoblastoma (Caro). Insect bites (Lahey Clinic).

DISCUSSION

DR. CARROLL F. BURGOON JR., Philadelphia: In the case of this child there has been considerable confusion. When he was first seen and the histologic sections were studied, Dr. Weidman made the diagnosis of histiocytoma. Subsequently the Armed Forces Institute of Pathology in Washington agreed with Dr. Weidman. Dr. Beerman made the diagnosis of mycosis fungoides. The patient was sent to the Lahey Clinic for cathode ray radiation, and the Clinic made a diagnosis of insect-bite reaction. The study of the patient revealed nothing except for the cutaneous findings. Several nodular lesions were irradiated and melted like butter, within a seven-day period, while control lesions remained unchanged. When the group at the Lahey Clinic saw him, the lesions had cleared markedly. However, he was not completely clear until the last month. As of this morning he still has intercostal lymphadenopathy, cervical lymphadenopathy, and epitrochlear lymphadenopathy.

DR. FRED D. WEIDMAN, Philadelphia: In diagnosis, insect bites are something like the situation of allergy—they are a wonderful "out." There is a wide range of tissue changes possible in insect bites, from acute phenomena such as a simple wheal or blister, down to the leucotic phenomena. In other words, depending on just which rung of the ladder you happen to be standing when the biopsy is done, you can bring in acute inflammation or you can bring in chronic inflammation, neoplasms, leucosis, and sarcoid, so that admittedly it is something that should be thought of and too much weight should not be placed on the sections in diagnosing insect-bite granuloma. Like everything else, one must take the whole picture into consideration. In looking at that section I never thought for a moment of insect bite. At the Academy meeting there were only two votes in favor of insect bites on this case. The others thought it a leucosis of some kind. I was naturally nonplussed with a diagnosis brought out like that that I had not thought of, and I am rather glad that these constitutional features have subsequently

developed—generalized lymphadenopathy and an additional lesion. I do not think we ought to jump to the conclusion that these are insect bites on the evidence we have. It is always better to depend on thoroughly established criteria for this or that rather than to grab at a straw in the wind which at a given time happens to be popular. I suppose we shall have to let this case go with the old saying that time alone will tell. But the way things have turned out, there are definitely changes which look like a leucosis. I am glad to know that in insect-bite granuloma there is a generalized lymphadenopathy.

Dr. Herman Beerman, Philadelphia: I saw this section during the American Board examination and I thought it represented mycosis fungoides unequivocally.

Dr. Donald M. Pillsbury, Philadlephia: Was this child tested for cat-scratch disease? I was amazed at the chronicity and variety of the cutaneous and lymph system manifestations that appear in that disease. I think it is not inconceivable that this might possibly be all part of cat-scratch disease.

Dr. John L. Fromer, Boston: I was responsible for the idea of insect bites. At the time we saw this patient he had no skin lesions whatsoever, a normal bone marrow, normal peripheral blood, and no adenopathy. He was well, eating well and gaining, and had a healing cutaneous lesion on the left elbow. The history showed that he came from a highly allergic family. The father and mother were both allergic individuals. The father reported marked reactions from insect bites; the lesions usually occurred on the exposed areas while he was at a summer camp in the country, and I thought that, in view of the lack of physical signs and other evidence of a lymphoma, we had best review the microscopic picture. This was done by Dr. Shields Warren who, before being given the history, thought we were dealing with an insect-bite granuloma.

As regards cat-scratch fever and cat-scratch disease, my own experience with this disorder is that only localized nodes are involved proximal to the injury and they usually become quite large. We had one such case recently and the intradermal tests were positive with a number of antigens specific for this disease furnished from various sources. It is a self-limited disease, as a rule, although it may be protracted. The important point is that a lymph node in a cat-scratch disease, I am told, presents a fairly definite pathologic picture, and this boy has had a lymph node biopsy which was negative for cat-scratch disease.

Reticulum Cell Sarcoma Associated with Generalized Neurodermatitis (Atopic), Atopic Cataract of the Left Eye and Dermatopathic Lymphadenitis, Considerably Improved by Treatment with Potassium Paraaminobenzoic Acid (KPAB). Presented by Dr. Reuben Friedman and (by invitation) Dr. Chris J. D. Zarafonetis, Philadelphia.

G. G., a white man aged 29, in 1943, shortly after the receipt of notification of his impending induction into the Armed Forces, developed patches of itching dermatitis on the dorsa of his hands. The eruption rapidly spread to other parts of his body, particularly the forehead, neck, and the cubital and popliteal areas. He was rejected by the Army. Thereafter the eruption flared and subsided periodically but never disappeared. Exacerbations were definitely associated with episodes of emotional stress.

In 1945 he developed a cataract of the left eye. He also developed pronounced enlargement of the glands in the inguinal and axillary regions. In 1948 the patient was hospitalized with a diagnosis of "atopic dermatitis" and subsequently discharged with little or no improvement. The patient, an intelligent, obviously tense, hyperkinetic and talkative person, was first seen by the presenter in March, 1951. He had a generalized, scaly erythroderma with patches of exudative dermatitis on the forehead, thighs, legs, and ankles. Thickening and lichenification were especially pronounced in the cubital and popliteal regions. There was decided thinning of the hair and eyebrows. The axillary, pectoral, and inguinal glands, particularly the latter, were greatly enlarged but not tender. They were firm, elastic, and not adherent to the overlying skin. The complete blood count on Sept. 11, 1951, revealed 11.2 gm. hemoglobin per 100 cc. (72%), 3,850,000 erythrocytes, 14,800 leucocytes, 43% neutrophiles, 20% lymphocytes, 3% monocytes, 33% eosinophiles, and 1% basophiles.

The patient's condition remained more or less unchanged until September, 1952, when he rapidly developed an ulcer on the left elbow, which "began as a mosquito bite." Examination

revealed an indurated, sharply marginated, crateriform ulcer 11 mm. in diameter. This gradually increased in size; the center became filled with a tightly adherent, black, necrotic slough, which in the course of several weeks became separated from its base, and the ulcer healed. Since September, 1952, the patient has continued to develop numerous similar necrotic ulcers on various parts of his body. These range in size from 1 cm. to 3 cm. or more in diameter. There is now only slight itching, on the arms.

On Oct. 15, 1952, biopsy was performed on two ulcers on the left arm. The material was submitted to Dr. Fred D. Weidman with a clinical diagnosis of mycosis fungoides. His diagnosis was "reticulum cell sarcoma."

Treatment with potassium paraaminobenzoate (KPAB) was instituted on Oct. 25, 1952. The patient received six doses daily of 30 cc. of 10% solution of KPAB, i. e., 18 gm. a day. In about three weeks the necrotic ulcers had shown considerable involution, being flatter, with less discharge and odor. Within a month, all of the lesions present at the beginning of therapy had healed, leaving more or less atrophic scars. New lesions, generally smaller and shallower, appeared, despite continued administration of the drug. These lesions, however, underwent involution much more rapidly than did the original ulcers which had shown little tendency to heal until KPAB therapy was begun. In view of the continued appearance of new lesions, the KPAB was increased from 18 to 21 gm. daily. This was well tolerated but did not completely suppress the appearance of sarcomatous lesions. In mid-February, 1953, the dosage of KPAB was further increased to 24 gm. daily. This was continued until Aug. 20, 1953, at which time the patient stopped the drug because he was completely free of lesions. By Sept. 8, there was one new lesion on the skin of the right postauricular area. Several new lesions appeared in early October, and treatment with KPAB, 24 gm. daily, was resumed on Oct. 15, 1953. He has remained on this dosage to the present time. The reticulum cell sarcoma process appears to be almost completely suppressed. In addition, there has been considerable improvement in the atopic dermatitis. Treatment with KPAB has been well tolerated; weight and blood values remain unchanged since October, 1952. He has continued to work throughout the course of his present illness and therapy.

DISCUSSION

Dr. Douglass A. Decker, Allentown, Pa.: What is the rationale of treatment with KPAB? Dr. Harry Arnold reported a severe neutropenia from the use of this drug.

Dr. Chris J. D. Zarafonetis, Philadelphia (by invitation): The rationale stems indirectly from our discovery that PABA increases metabolism greatly. Knowing that, we decided to try it in leukemia, because we felt that the cells were abnormal and that if we could step up the metabolism, then perhaps the cells would not be able to withstand that change of pace. With severe cases of chronic myelogenous leukemia we saw patients with cutaneous infiltrations whose lesions disappeared while they were on PABA. We went to Dr. Curtis who is treating some of the lymphoblastomas, and that led to this. As far as toxicity is concerned, I should like to refer back to the Typhus Commission days when we were treating epidemic typhus, using nothing but crystalline PABA. We observed nausea and diarrhea; we thought also some leucopenia, but when that study was finished we found no more leucopenia in the cases that received PABA than in the cases that were not treated with PABA. I have followed close to 500 patients from one to five years in lupus erythematosus and other diseases. There are times when we get a leucopenia, but I have not yet had to stop treatment of 12 gm. or so a day because of the blood picture. I have written to authors who have claimed to have seen toxic manifestations, but unfortunately they have not felt like submitting data. I do believe that the incidence of agranulocytosis would be extremely rare. I do not mean that it will never occur, but I have yet to see a proved case of agranulocytosis due to PABA.

Dr. Jacob H. Swartz, Boston: For the past five years I have had a patient with mycosis fungoides on sodium PABA in doses of 2 gm. a day. She has been studied very carefully by Dr. William Castle of Boston. In that particular case we have been unable to stop the PABA because of relapse of the tumor stage. It produced no ill effects except an occasional false positive test for sugar in the urine, with a normal blood sugar. There is no question in my mind that in the few cases in which PABA was administered some of the tumor lesions have either diminished or disappeared, but we have no case that we can say has been cured by sodium PABA.

It does seem to control the disease temporarily. I am interested in the cataracts in this patient. In the series of atopic dermatitis cases with associated cataracts that we studied, most occurred in the teens, and usually with a history of having had infantile eczema. The late Dr. Terry of the Massachusetts Eye and Ear Infirmary stated that these cataracts are of a nutritional deficiency type, and we have found that these cases have been on a very restricted diet for a long time because of the eczema.

DR. G. E. CRAIG, Montreal: In patients to whom we have given large doses of PABA there has been nausea and I wonder whether there is any easier way of giving large doses.

DR. CHRIS J. D. ZARAFONETIS, Philadelphia (by invitation): We went through a great deal of trial and error to find out how best to give PABA. We have used sodium paraaminobenzoic acid for a long time and found that in these patients, such as the one you saw, we frequently increased the edema and the discomfort, at least for a while. That is why we made up the potassium salt, and have used it almost exclusively ever since. We take 100 gm. of the powder and dissolve it in a quart of water. The patients can refrigerate it and use anything they want as a chaser, but almost invariably they drink it straight, with water as a chaser. When they have nausea, I have them stop the drug, and then resume it, rather than force them to take it at that time. We have rarely had a patient who could no take KPAB. We use the salt in solution, because it is much better than tablets; potassium salt in tablet form gives abdominal cramps.

DR. GEORGE MORRIS, Boston: Both patients have had a diagnosis of atopic neurodermatitis. I have seen many cases of atopic neurodermatitis, and not one has developed the picture of reticulum cell sarcoma. I wonder whether atopic neurodermatitis in these cases was correct; or is it, rather, a nonspecific type of dermatitis associated with sarcoma.

Mycosis Fungoides Treated with Cathode Ray. Presented by DR. JOHN L. FROMER, Boston and DR. HUGH M. CRUMAY, Harrisburg, Pa.

DISCUSSION

DR. DONALD M. PILLSBURY, Philadelphia: This patient, whom we have not seen for about two years, had a considerable trial with various types of roentgen therapy with various doses on different lesions, without any effect. I am sure he would not have responded to any type of ordinary x-ray therapy.

DR JOHN L. FROMER, Boston: The patients in our series have had spray or x-radiation to the point of tolerance in the judgment of the dermatologists or radiologists who have referred these cases to us. The reason for response with another form of ionizing therapy is unknown to us except that the distribution in depth for cathode ray is different from that of x-radiation. I should add further that in a three-year follow-up with the present technique we have observed a change in the hemogram in 40% of the patients. Although most of these changes are not serious, and we hope are reversible, nevertheless they still exist, and we have modified our treatment. We have treated 20 patients with mycosis fungoides. We plan to decrease the voltage from 2.5 to 1.5 MEV and localize the ionization to the first 5 to 6 mm. of skin. Later, the patients may return for local shielded therapy to any lesion that persists.

Reticulohistiocytoma Cutis? Nevoxanthoendothelioma? Presented by DR. BERNARD L. KAHN and (by invitation) DR. MARGARET GRAY, Philadelphia.

Lipoid Reticuloendotheliosis? Nevoxanthoendothelioma? Presented by DR. CARROLL F. BURGOON JR., Philadelphia.

DISCUSSION OF TWO PRECEDING CASES

DR. FRANCIS A. ELLIS, Baltimore: I would classify both these cases as nevoxanthoendothelioma. There has been a tendency recently to change this terminology, but I adhere to the old term of nevoxanthoendothelioma. The history is compatible with this condition. I should like to mention a patient that I saw who developed hundreds of cutaneous lesions. He developed normally until the lesions were fully developed, and then his mental development stopped at that stage, so that at the age of 8 or 9 his mentality was about that of a 2½-year-old child.

DR. HERMAN BEERMAN, Philadelphia: I think I am responsible for the reticulohistiocytoma diagnosis. Dr. Gray made the diagnosis of nevoxanthoendothelioma. On numerous occasions I

have stated that these cases should be studied as abortive types of Hand-Schüller-Christian syndrome, as Thannhauser some time ago pointed out. We reported a case with ocular involvement. Dr. Ellis, I believe, also had a case with ocular involvement. Dr. Lamb and others also had a patient with visceral manifestations.

DR. LEON BABALIAN, Portland, Me.: In these lesions, clinically suggestive of nevoxanthoendothelioma, a special stain with one of the basic aniline dyes sometimes shows the existence of mast cells. These lesions then deserve the name of mastocytoma, or what French authors call *réticulose mastocytaire*. I think the cases presented today could be studied along these lines, whatever may be their exact clinical aspect: urticarial or not, xanthelasmoid or not. (Kierland, R. R., and Stegmaier, O. C.: ARCH. DERMAT. & SYPH. **62**:28-32 [July] 1950; Duperrat, and de Sablet: *Bull. Soc. franç. dermat. et syph.* **59**:250 [May-June] 1952.)

DR. GEORGE C. ANDREWS, New York: Were the biopsies done from the lesions on the face? Because those lesions look a great deal like adenoma sebaceum.

DR. MARGARET GRAY, Philadelphia (by invitation): They were taken from the face—both the papules and the flat lesions.

Chronic Arsenical Poisoning with Arsenical Keratoses. Presented by DR. DONALD M. PILLSBURY, Philadelphia.

DISCUSSION

DR. DONALD M. PILLSBURY, Philadelphia: Has anyone seen improvement in hyperpigmentation or keratoses due to the ingestion of inorganic arsenical compounds, upon the use of dimercaprol (BAL)? We have seen no change at all.

DR. MAURICE J. COSTELLO, New York: Dr. Andrews stated that he thought that patients with arsenical keratoses involving the palms and soles should receive dimercaprol, not necessarily for the immediate therapeutic benefits but because they may develop fewer lesions later on. Recently I gave a patient two courses without any apparent improvement at the time, and prior to that time I had removed at least 30 epitheliomas. In the past two years she has developed one; so I think we can judge from that case that dimercaprol should be a routine procedure in the treatment of these people.

DR. G. E. CRAIG, Montreal: I can report on one case we treated in which the symptoms of severe itching which the patient suffered stopped with the use of dimercaprol.

DR. GEORGE C. ANDREWS, New York: Although it has been stated that dimercaprol is of use only in acute arsenical intoxication and of no use in chronic arsenical poisoning, the impression from my experience is that dimercaprol is of some benefit is chronic cases, probably in preventing these lesions. We are trying to determine the quantity of arsenic in the skin by making it radioactive and testing it that way. I am interested in what happens to these people with arsenical keratoses. Of what do they die? A number have died of carcinoma of the intestines, and I have wondered whether those carcinomas of the intestines were arsenical in origin. We know that carcinoma of the bladder may be arsenical in origin. I think we should keep a record of the cause of death in patients who have arsenical keratoses.

DR. DAVID BLOOM, New York: In a case of arsenical keratosis on the palms following therapy for dermatitis herpetiformis, I considered the treatment with dimercaprol useless, since chemical examination of the verrucous lesions by Dr. Alexander Gettler did not reveal any pathologic quantity of arsenic.

DR. HERBERT MESCON, Boston: In our patients with arsenical poisoning we exhausted almost all methods of demonstrating small quantities of arsenic in the skin, but the quantities are so minute that they cannot be detected with the present methods. The quartz spectrograph (sensitive to 0.001% As) and the Gutzeit method for arsine, using HgBr as a detector (sensitive to 1 γ), were unable to detect arsenic in the skin of our cases. We are at present running sulfhydryl stains in an attempt to demonstrate the sulfhydryl group (SH) bound by the arsenic.

Juvenile Acanthosis Nigricans vs. Pseudoacanthosis Nigricans? Melanoderma Toxica? Presented by DR. M. H. SAMITZ and DR JACK WEINER, Philadelphia, and (by invitation) DR. E. MONTERO, Philadelphia.

Ectodermal Defect. Classification? Ichthyosis? Possible Congenital Pulmonary Lesions. Presented by DR. DAVID M. SIDLICK, DR. MARVIN GREENBERG, and (by invitation) DR. RAYMOND KRAIN and DR. HAROLD COLBURN, Philadelphia.

Ectodermal Defect. Diagnosis at Birth, Epitrichial Exfoliation. Presented by Dr. David M. Sidlick, Dr. Marvin Greenberg and (by invitation) Dr. Raymond Krain and Dr. Harold Colburn, Philadelphia.

Panhypopituitarism. Postmyxedematous Sclerosis vs. Scleroderma (Lower Legs). Presented by Dr. Donald M. Pillsbury, Philadelphia.

Anetoderma. Presented by Dr. M. H. Samitz, Dr. Jack Weiner, and (by invitation) Dr. H. Pomerantz, Philadelphia.

Linear Lichen Planus (?). Presented by Dr. Bertram Shaffer and (by invitation) Dr. Raymond Krain and Dr. Harold Colburn, Philadelphia.

Lichen Sclerosus et Atrophicus. Presented by Dr. Carmen C. Thomas Philadelphia.

Lichen Sclerosus et Atrophicus. Presented by Dr. Herman Kline, Atlantic City, N. J.

Keratosis Follicularis (Darier's Disease). Presented by Dr. Miriam Reed, Princeton, N. J.

Pityriasis Rubra Pilaris. Presented by Dr. Henry Harris Perlman, Philadelphia.

Mycosis Fungoides with Transition to Reticulum Cell Lymphoma. Presented by Dr. Meyer L. Niedelman, Philadelphia.

Mycosis Fungoides. Presented by Dr. Carmen C. Thomas and (by invitation) Dr. Donald Madden, Dr. Samuel Perlstein and Dr. Edward Karamanoukian, Philadelphia.

Lymphoblastoma. Presented by Dr. Carmen C. Thomas, Philadelphia.

Pili Annulati. Presented by Dr. A. J. Paul, Philadelphia (by invitation).

Livedo Reticularis? Vascular Nevi? Presented by Dr. Carroll F. Burgoon Jr., Philadelphia.

Phlegmonous Insect-Bite Reaction? Presented by Dr. Carroll F. Burgoon Jr., Philadelphia.

BRONX DERMATOLOGICAL SOCIETY

Nathan Sobel, M.D., *President*

Henry Silver, M.D., *Secretary*

Feb. 18, 1954

Use of Monobenzyl Ether of Hydroquinone (Agerite Alba) in Dermatology. Presented by Dr. Julius H. Pollock.

DISCUSSION

Dr. Alexander A. Fisher: In October, 1949, I presented before this Society a case of chloasma which I treated with 5% monobenzyl ether of hydroquinone (Agerite Alba) in Laviderm (a preparation containing palmitic acid ester of cetyl alcohol, isopropyl palmitate, and triethanolamine). Laviderm was a base that Dr. Pollock recommended. Two weeks after treatment was begun the patient had a marked dermatitis on the face. Patch testing implicated the monobenzyl ether of hydroquinone and not the laviderm base. Strangely enough, after the dermatitis subsided the chloasma disappeared. In another case a severe dermatitis due to allergic sensitization to the monobenzyl ether of hydroquinone developed, but after the dermatitis cleared the chloasma also cleared. Dr. Spencer had also mentioned several cases in which the therapeutic result was good in spite of the fact that the patient developed sensitization to the monobenzyl ether of hydroquinone.

Dr. Rudolf L. Baer: This Society owes thanks to Dr. Pollock for having been among the first, if not the first, to try treating cosmetically the objectionable, hyperpigmented areas with monobenzyl ether of hydroquinone in creams. Another member of this Society, Dr. Franz Herrmann was, I believe, the first to show that hydroquinone systemically administered produces depigmentation in frogs, many years before the depigmenting action of this compound was demonstrated in another species.

As far as irritations due to this compound are concerned, one must sharply differentiate between its primary irritant action and its specific allergenic sensitizing capacity. When irritation due to its primary irritant effect occurs, treatment can be continued with weaker concentrations; but when irritation due to allergic sensitization occurs, the use of this material must, as a rule, be discontinued for good.

When Dr. Pollock first reported on his clinical trial several years ago, he warned of the possibility of producing depigmentation of the normal skin surrounding the hyperpigmented areas. I have not observed any such undesirable effect. Apparently this depigmenting effect on normal skin occurs in Negro patients but not in white patients.

An interesting case is a patient of mine, a girl about 15 years old, who had a grayish-brown, pigmented nevus covering the left side of her neck. This lesion, which was particularly objection-

able because it looked as if she had not washed properly, had been present all her life, but responded well to treatment with monobenzyl ether of hydroquinone cream. It had practically disappeared and had stayed away for several months until three days after she went to Florida and exposed herself to much sunlight, when the pigmentation recurred. You can gather from this that patients who have had this type of treatment and who have responded well should be advised to use a sun-protective cream or other preparation on the treated areas.

One substance which is of interest in connection with Dr. Pollock's presentation is para-hydroxypropiophenone. I have had no personal experience with it, but Dr. Charles Grupper of Paris told me that this material is superior to monobenzyl ether of hydroquinone in Riehl's melanosis. I do not recall whether this substance was administered by mouth only or also topically.

DR. CHARLES R. REIN: Dr. Charles Grupper of Paris has used this material both by oral and local routes in the treatment of hyperpigmentation. He was kind enough to supply us with these materials, but, unfortunately, our results were unsatisfactory.

DR. FRANZ HERRMANN: In our early experiments—just quoted by Dr. Baer—it was diiodohydroquinone and to a lesser degree also diiodotyrosine which interfered with the physiologic formation of pigment in Salamandra maculosa and in Ambystoma trigrinum (axolotl) during transformation of the aquatic larvae into terrestrial animals (*Acta dermat.-venereol.* **20**:1, 1939).

Simultaneously, not unlike thyroxine, diiodohydroquinone as well as diiodotyrosine distinctly accelerated the metamorphosis from the aquatic into the terrestrial stage of the animals. In view of the modern concepts of melanogenesis, it may be worth while recalling that these two chemicals build up thyroxine.

DR. NORMAN B. KANOF: We tried Grupper's material both by mouth and locally and we did not get the results reported. We used monobenzyl ether of hydroquinone, 0.5%, in a soap furnished us by Dr. Herman Sharlit and got what we thought were fair results. We used it over a period of several months without any sensitization in the cases we tried.

DR. JULIUS H. POLLOCK: It has been impossible to cover everything because of the shortness of time and lateness of the hour. Dr. Fisher's remarks about the patients he originally presented before this Society when I first discussed this method of depigmentation are certainly timely in showing that we should not be too hasty to judge the results of therapy but rather that we should withhold appraisal of a therapeutic agent in terms of time, patience, and patients. It is now definitely known that the contact dermatitis one sometimes encounters is not the cause of the depigmentation. As a matter of fact, certain patients, especially Negroes, may become more pigmented.

I want to thank Dr. Baer for his kind and pertinent remarks. Apropos of his observations and Dr. Fisher's, we should note that the monobenzyl ether of hydroquinone may cause a dermatitis due to a primary irritant. Here the patch test is negative, and often when the dermatitis subsides the monobenzyl ether of hydroquinone can again be utilized with further good results. We think the high concentrations and improper vehicles are factors here. But the patient may develop a real contact dermatitis regardless of length of use or concentration. In such case the patch test will be positive, and further use of the material is contraindicated; thus the patch test is of value in guiding one as to the type of reaction encountered. It may also be mentioned that not only is it good policy to protect the treated area from the sun after a good result is obtained, but the sun-screening lotion should also be used to protect adjacent areas treated, to prevent, if possible, depigmentation in normal skin.

As Dr. Herrmann has mentioned, clinically it has been found that sometimes hyperpigmentation may occur after use of these compounds. It is believed that the hyperpigmentation thus found may be due to the fact that the material used is not a pure form of monobenzyl ether of hydroquinone, but contains hydroquinone, and hence some kind of dark compound is formed which adheres to the skin.

From our presentation based on our experience and the discussion brought out here we believe that monobenzyl ether of hydroquinone is not a material which can be used without a certain amount of risk of obtaining untoward results. When the material is marketed commercially, as it has been already, it will not be a far cry from "counter prescribing," and when the patient can use this material uncontrolledly, bizarre results will surely follow.

I believe that in monobenzyl ether of hydroquinone we have the best depigmentary agent developed to date, but I believe that the product is not ready for commercial use and widespread application for several reasons. It should still be used in a research or experimental sense until the difficulties of peculiar pigmentary side-reactions and contact and primary irritant dermatitis are resolved.

Lichen Scrofulosorum. Presented by DR. HANS H. BIBERSTEIN.

Lichen Planopilaris with Extensive Alopecia. Presented by DR. ALEXANDER A. FISHER.

Kaposi's Sarcoma in a Woman. Presented by DR. JOHN GARB.

Fixed Drug Eruption? Presented by DR. ABRAHAM J. ORFUSS.

Parapsoriasis Guttata. (Varioliformis.) Presented by DR. DAVID B. BALLIN.

Sturge-Weber Syndrome (Encephalotrigeminal Angiomatosis) Associated with Unilateral Cutaneous and Osseous Sarcoidosis. Presented by DR. DAVID BLOOM.

Hyperpigmentation Treated with Monobenzyl Ether of Hydroquinone. Leukoderma. Presented by DR. JULIUS H. POLLOCK for DR. LUDWIG SCHWARZSCHILD (by invitation).

Dyskeratosis Congenita with Pigmentation; Dystrophia Unguium, and Leukoplakia Oris. Presented by DR. JOHN GARB.

Lupus Erythematosus (Systemic?); Chronic Nephritis. Presented by DR. ALEXANDER A. FISHER.

THE METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Fred F. Feldman, M.D., *President*

Irving A. Lewe, M.D., *Vice-President*

Harold Price, M.D., *Secretary*

March 23, 1954

Lymphocytic Infiltrate of the Skin. Presented by DR. MURRAY ZIMMERMAN.

Since August, 1953, there have been recurrent reddish plaques over both zygomatic areas, which have cleared with the local use of iodine. No subjective symptoms have been present.

The physical examination revealed erythematous, slightly raised, dusky plaques which pale on pressure, over both zygomatic areas. No atrophy was present.

The histologic picture fits the description of lymphocytic infiltrate of the skin perfectly.

Quinacrine (Atabrine) treatment was started on March 23, 1954.

DISCUSSION

DR. MURRAY ZIMMERMAN (Slide): The epidermis appears normal. Just under the epidermis, a little edema and some degeneration of connective tissue are noted. There is a marked, very heavy infiltrate which is centered in the midcutis, especially around blood vessels, which are somewhat edematous. The infiltrate is composed almost entirely of small round cells which have taken a heavy stain, which I personally feel is abnormally heavy, like some form of blood dyscrasia. These round cells are set on what is distinctively reticulum. They are like beads on a string, with reticulum around and through them.

DR. MEYER BERKE: Assuming that this lymphocytic infiltration is a separate entity, this patient presents a clinical picture and histology which fits in with what we have been calling in the past lupus erythematosus profundus. I am not saying that lymphocytic infiltrate is not a separate entity. Certainly the histologic and clinical findings are grossly similar to what has been found in lupus erythematosus profundus, so-called lymphocytoma cutis, and erythema perstans. Do we gain much by applying still another name without having any further clue as to etiology?

DR. CHARLES SHERTER: Clinically, the lesion is very striking and resembles the so-called facial granuloma with eosinophilia. I recall that Hermann Pinkus had a case in which there was striking ear lobe involvement that was almost an exact copy of that found in this patient. Further histologic examination might disclose that there is more eosinophilic infiltration in some areas than others to lend support to the diagnosis of a facial granuloma with eosinophilia.

DR. FRED F. FELDMAN: I feel that Dr. Zimmerman's case is the most typical example of this condition, both clinically and histologically, that I have seen. However, I would consider my understanding of this condition meager, as it is based on experience with only six cases, three

of which were confirmed by Dr. Max Jessner. I would not attempt to make this diagnosis on the basis of the histopathologic findings alone. I think that correlation between the clinical and microscopic picture is necessary. Chronic discoid lupus erythematosus, polymorphous light eruptions, erythema perstans, and fixed drug eruptions appear to me to be the most likely conditions that may be confounded with lymphocytic infiltration of the skin. Clinically, granuloma annulare and sarcoid may occasionally be considered in the differential diagnosis. Spontaneous remissions of the lesions, sometimes within a few days, appears to be an important feature of this dermatosis.

Idiopathic Hyperlipemic Xanthomatosis. Presented by DR. MURRAY ZIMMERMAN.
Parapsoriasis. Presented by DR. EDWARD L. MURPHY and DR. VINCENT P. BURBY (by invitation).
Case for Diagnosis. Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.
Case for Diagnosis. Leukemic Nodule? Presented by DR. ERNEST THOMAS FOX.
Herpes Progenitalis. Presented by DR. STANTON B. MAY for discussion of therapy.
Granuloma, Type Undetermined. Presented by DR. MURRAY ZIMMERMAN for diagnosis.
Case for Therapeutic Suggestions. Presented by DR. STANTON B. MAY and DR. ALFRED GRAVES (by invitation).

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Feb. 10, 1954

Nodular, Nonsuppurative Panniculitis. Presented by DR. MAURICE M. TOLMAN, Boston, and (by invitation) DR. JOHN H. COX, Boston.

M. R., a 24-year-old sailor, in a period of six months had developed three slightly tender, indurated, red, deep-seated plaques on the anterior surface of the thighs. The first lesion subsided spontaneously in three weeks. The second broke down, drained watery material, and healed spontaneously. The third was subsiding at the time of presentation.

Examination revealed an irregular, dusky, bluish area on the anterior aspect of each thigh. There was a thin, atrophic, band-like scar on the upper anterior surface of the right thigh. The most recent lesion still presented a moderate degree of infiltration.

Biopsy presented characteristics of nodular nonsuppurative panniculitis (Weber-Christian disease).

DISCUSSION

DR. JOHN L. FROMER, Boston: We had a patient in my last year of military service who presented this type of lesion and in whom we could produce a lesion similar to this by local application of cold. If an ice cube were applied to any of the exposed areas, within 24 to 36 hours tumefaction and then breakdown of the tissue occurred, followed by healing without much scarring. Pathologists agreed that the microscopic picture was consistent with Weber-Christian disease.

Xanthoma Tuberosum, Multiple Lesions. Presented by DR. JULIUS PICARD, Fall River, Mass.
Nonlipoid Histiocytosis. Presented by DR. CHESTER N. FRAZIER, Boston.
Lupus Vulgaris. Presented by DR. JOHN ADAMS JR., Boston.
Lupus Vulgaris. Presented by DR. JOHN ADAMS JR., Boston.
Lupus Vulgaris. Presented by DR. ROBERT F. TILLEY, Boston.
?Nodular Vasculitis. Presented by DR. PAUL J. CATINELLA, Boston.
Malignant Dyskeratosis. Presented by DR. D. FOLAN, Boston (by invitation of DR. BERNARD APPEL, Lynn Mass.).
Lichen Sclerosus et Atrophicus. Presented by DR. ROBERT H. GOLDFARB, Boston.
Necrobiosis Lipoidica Diabeticorum. Presented by DR. MAURICE M. TOLMAN, Boston.
Dermatitis Medicamentosa (Phenolthalein). Presented by DR. WILLIAM J. MACDONALD, Boston.
Lupus Vulgaris. Presented by DR. JOHN ADAMS JR., Boston.
?Sarcoid. Presented by DR. WILLIAM J. MACDONALD, Boston.

News and Comment

SCIENTIFIC EXHIBITS

The A. M. A. Archives of Dermatology and Syphilology is pleased to introduce in this issue a new feature called "Scientific Exhibits."

This feature attempts to preserve in more permanent form some of the instructive Scientific Exhibits that are presented at the Annual Meetings of the American Medical Association. Although thousands of physicians attend the Annual Meetings, viewing and studying the Scientific Exhibits at first hand, other thousands are unable to attend. For the first time, the latter group is now given the opportunity to see the exhibits reproduced in the pages of the various A. M. A. Specialty Journals.

While it is at present impossible to publish all the Scientific Exhibits presented at each Annual Meeting of the American Medical Association, it is feasible to select a representative few for the purpose of introducing the new feature to the readers of this periodical. Should "Scientific Exhibits" be well received, it is planned to expand the new department in future issues of the A. M. A. Archives of Dermatology and Syphilology.

ANNOUNCEMENTS

Fifth Pollitzer Lecture.—The Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School announces that the fifth Sigmund Pollitzer Lecture will be given by Dr. P. B. Medawar on Monday, Nov. 15, 1954, at 4:30 p. m., in the Psychiatric Amphitheater of Bellevue Hospital, 400 E. 30th St., New York. Dr. Medawar is Professor of Zoology at the University of London. The title of his talk will be "Skin Transplantation and the Homograft Problem."

NOTICE

The Annual Meeting of the American Medical Association will be held in Atlantic City, June 6-10, 1955. Physicians hoping to take part in that meeting should communicate with their Section officers as early as possible. Deadlines have been set, after which applications will be considered only if there are withdrawals in the program.

DEADLINE FOR SECTION PAPERS, Dec. 15, 1954

DEADLINE FOR SCIENTIFIC EXHIBIT, Jan. 10, 1955

Communications should be addressed to the following:

Section on Dermatology and Syphilology

Secretary—J. Walter Wilson, M.D., 3875 Wilshire Blvd., Los Angeles 5

Representative to Scientific Exhibit—Samuel M. Bluefarb, M.D., 30 N. Michigan Ave., Chicago 2

CORRECTION

In the article, "Histology of Lupus Erythematosus," by Drs. Francis A. Ellis and William R. Bundick, in the September issue of the Archives the columns were reversed in the lower portion of Table 4 (p. 318) and the data now given under "Hist." should appear under the heading "Clin." and vice versa. An asterisk should also follow "Hist." in the column heading, and a footnote to the Table should read: * Histologic diagnosis of any of the three types of lupus erythematosus.

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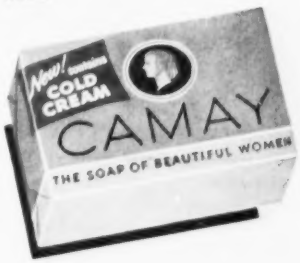

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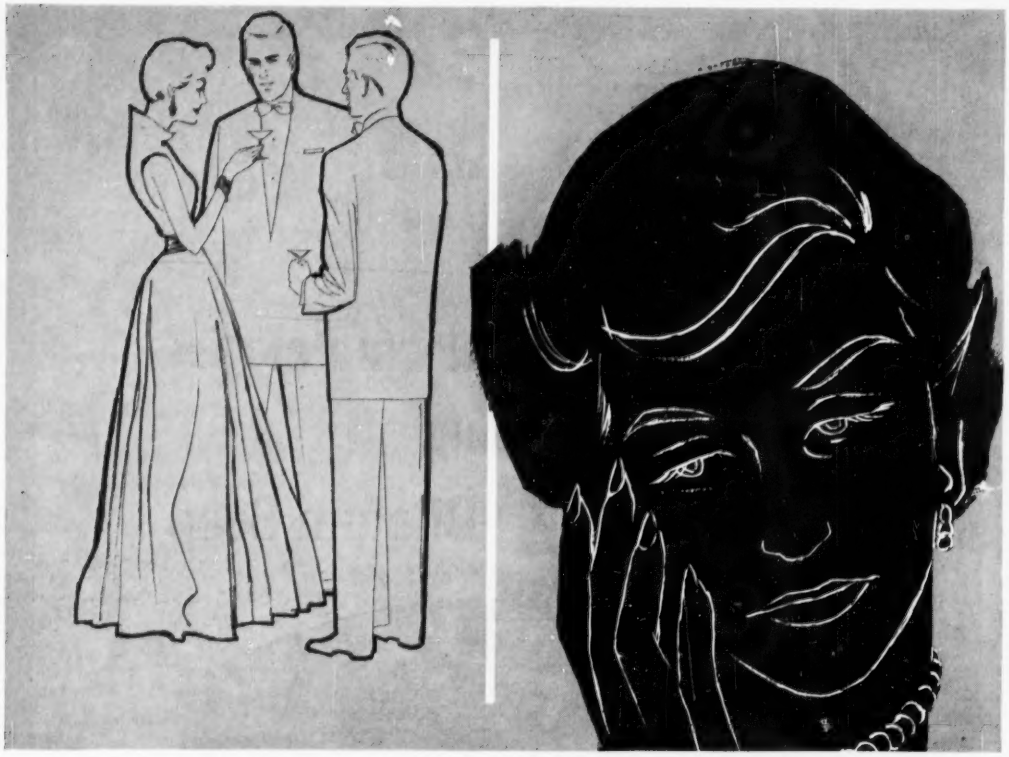

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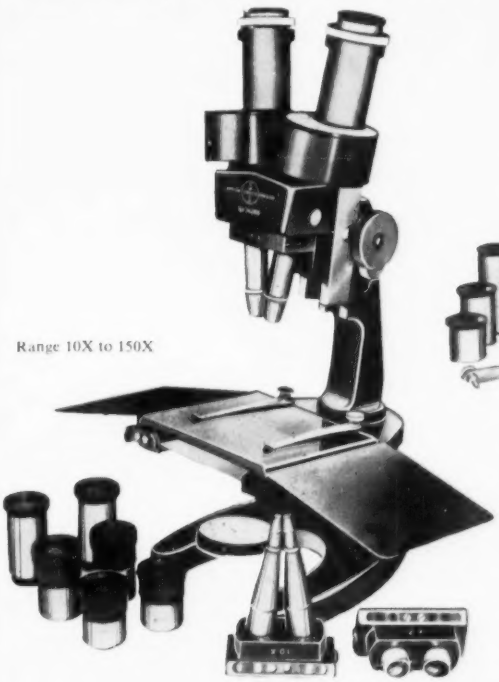

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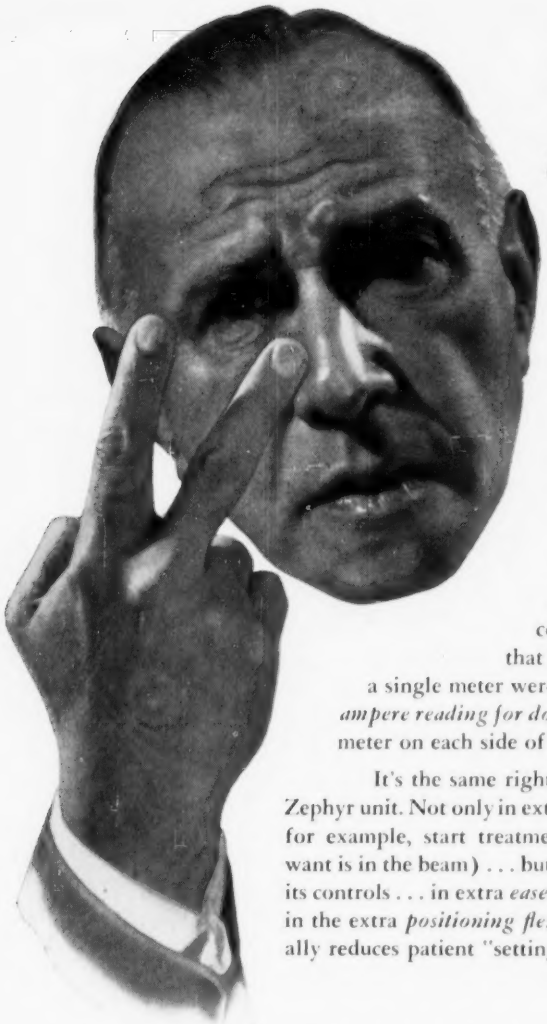

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